THE DEVELOPMENT OF PD(II)/SULFOXIDE-OXAZOLINE CATALYZED ALLYLIC C—H FUNCTIONALIZATIONS

BY

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DISSERTATION

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Professor Thomas B. Rachfuss

ABSTRACT

Pd-catalyzed allylic C—H functionalization is a powerful platform to stereoselectively and regioselectively convert terminal olefins (typically considered inert under most reaction conditions) into higher value chemical commodities. At the outset of this research program, several challenges with allylic C—H functionalization included: poor to moderate enantioselectivities in stereoselective transformations, and limited scope of functionalization partners. This thesis describes effort towards the development and application of Pd(II)/sulfoxide-oxazoline (Pd(II)/SOX) catalysis towards addressing these challenges.

The first chapter outlines the development and application of Pd(II)/SOX catalysis towards the difficult challenge of asymmetric allylic C—H alkylation. Critical to this strategy was investigations into the cis-SOX ligand framework—a diastereomer of the SOX ligand which was theorized to have greater enantiocontrol around the intermediate π-allyl. This chapter describes the development and application of this system to α-nitrotetralones, a versatile precursor to amino ketones and amino alcohols. The chapter also details efforts into addressing challenging β-ketoester nucleophiles, and the elucidation of a key ligand structural feature important for enantioselectivity.

The second chapter outlines the development and application of Pd(II)/SOX catalysis towards allylic C—H aminations with basic secondary amines. Intermolecular C—H amination is typically limited to doubly or singly protected nitrogen species, allowing only for protected ammonia or primary amine installation. Typically, basic amines are liable to bind tightly to the electrophilic metal catalysts for C—H cleavage and can inhibit useful reactivity. An amine quaternization strategy was applied to basic secondary amines, which allowed for a slow release

of the free amine. This slow release allowed for functionalization to occur with no detrimental inhibition of the electrophilic Pd(II) center. This strategy was applied to a variety of secondary amines cores, forging pharmaceutically relevant tertiary amine products. In addition, the mild selective allylic functionalization was tolerant of numerous functionalities considered traditional electrophiles for amino functionalization. Finally, several tertiary amine drugs and drug derivatives were synthesized, demonstrating the synthetic utility of this transformation.

ACKNOWLEDGMENTS

First and foremost, I'd like to thank my research advisor, Professor M. Christina White. I have benefited greatly from her vision and energy throughout the years, and she has pushed me to develop my own skills far beyond I could have ever imagined. I will always be grateful for all opportunity she gave me to do chemistry in an exhilarating and fun environment.

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Finally, I'd like to thank my family who have dealt with me living so far from home for way too long. Their constant support over the years and encouragement to pursue my dreams pushed me throughout all these years.

To my mother, Ayesha Luz Morales

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CHAPTER 1: Asymmetric Allylic C—H Alkylation *via* Pd(II)/cis-SOX catalysis

Acknowledgements

This chapter has been partially adapted from the research article "Asymmetric Allylic C–H Alkylation via Palladium(II)/cis-ArSOX Catalysis" (Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. J. Am. Chem. Soc. **2018**, *140*, 10658—10662).

This work is a collaborative effort. The optimization for nitroketones was done by Wei Liu and is included for context. The optimization for benzofuranones and the scope with benzofuranones and furanones was done by Wei Liu and Stephen Ammann and is not included in this thesis.

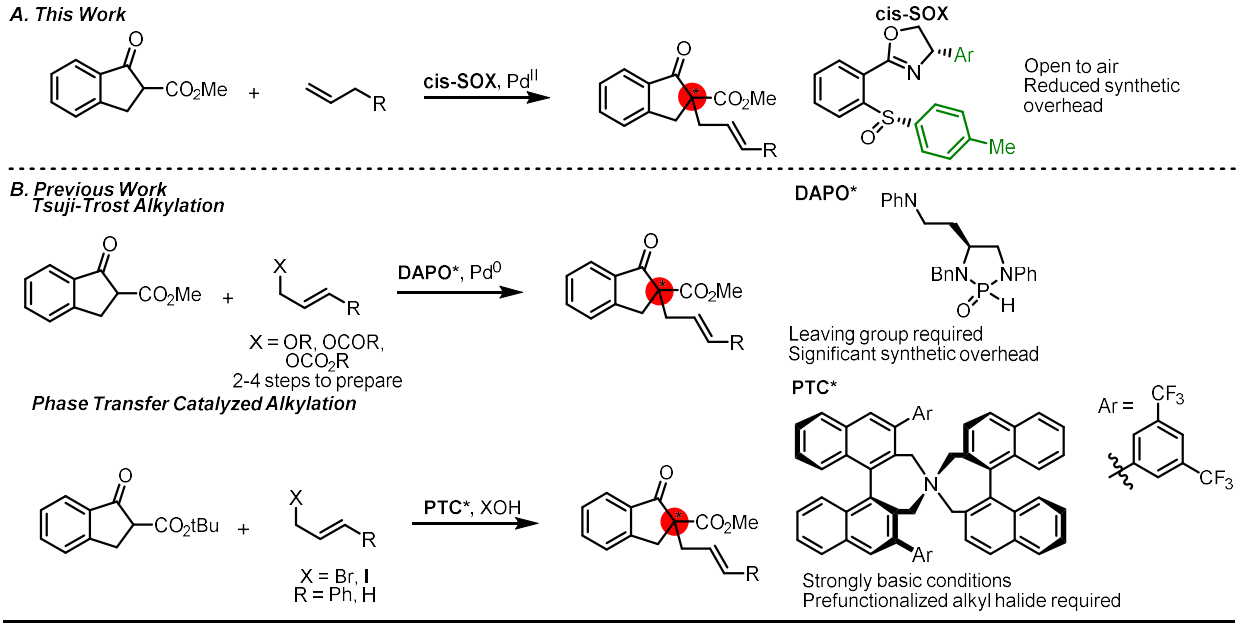
1.1 Introduction

The enantioselective synthesis of quaternary centers still represents a challenge in synthetic organic chemistry.[1,2] One attractive route to these motifs would involve an asymmetric allylic C—H alkylation of terminal olefins and activated carbon nucleophiles (Figure 1.1.1A). Such an approach would take advantage the selective methods of installing terminal olefins in complex molecule settings as well as the abundance of simple terminal olefins in bulk commodity chemicals.[3–5]

Traditionally, similar transformations have been achieved using the Tsuji-Trost asymmetric allylic alkylation (AAA), which involves the generation of a Pd-π-allyl from allylic acetates, followed by nucleophilic attack from an activated 3° carbon nucleophile (Figure 1B) and the phase transfer catalyzed (PTC) allylic alkylation of 3° carbon nucleophiles and allylic halides.[6–8] These methods utilize stereochemically defined allylic oxygenates (or halides), which require significant synthetic overhead to install in a complex molecule setting.[9] To date, these transformations have been only applied to simple allylic functionality, presumably due to this

limitation. In addition, the PTC allylic alkylation has only been demonstrated for two examples, a styrenyl and a symmetric substrate. The selectivity (e.g. regioselectivity and enantioselectivity) with more complex allylic substrates is unclear.

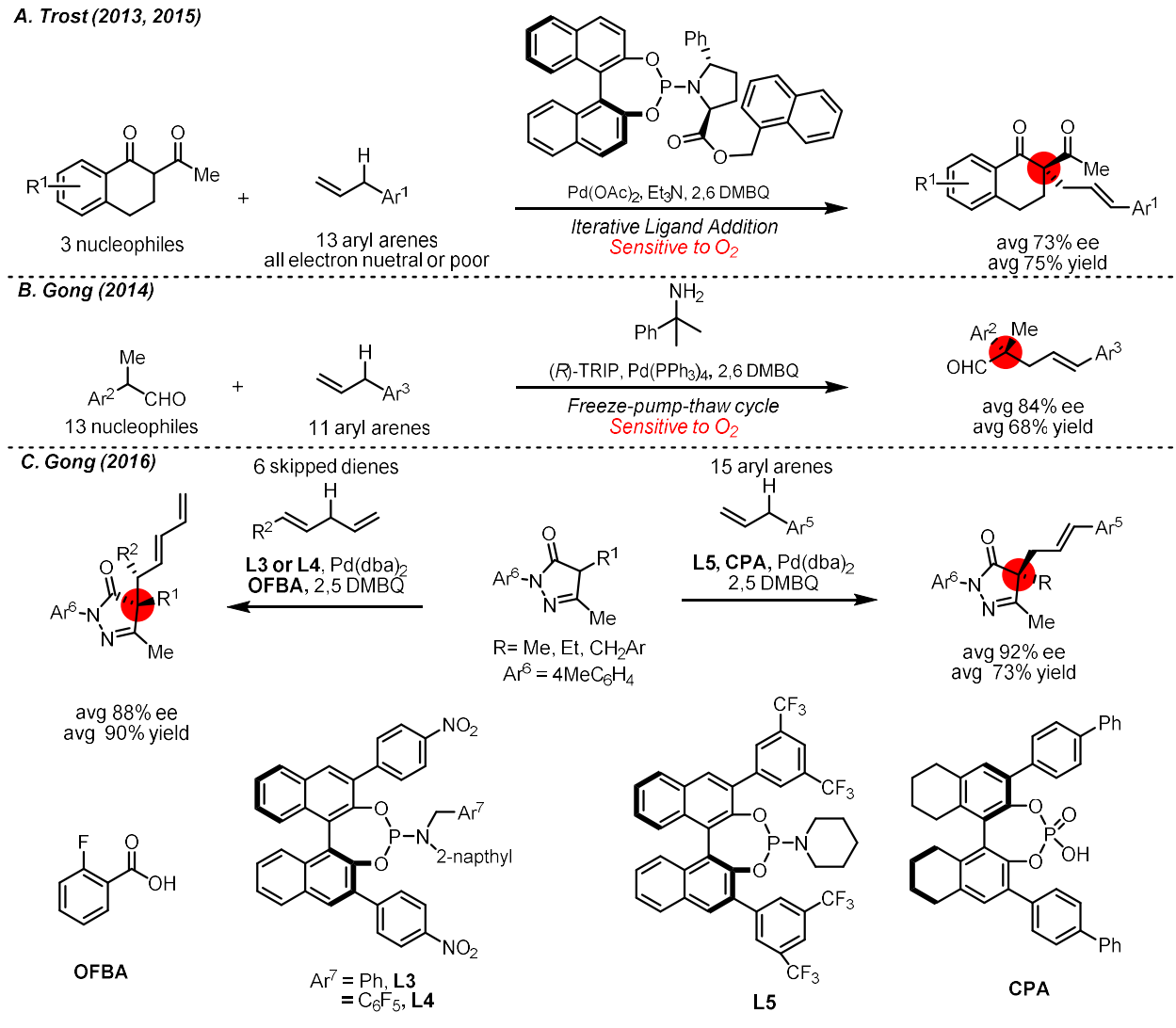
Fig 1.1: Proposed asymmetric allylic C—H alkylation



Current asymmetric allylic C—H alkylation methodology suffers from oxidatively unstable ligands, moderate levels of enantioselectivity, and poor generality. In 2013, Trost and coworkers disclosed the alkylation of electron poor allyl arenes with a 1,3 dicarbonyl species derived from tetralone with only moderate levels of enantioselectivity (Figure 1.1.12A).[10,11] Furthermore, the phosphoramidite ligand must be added iteratively, presumable due to oxidative instability. In 2014, Gong and coworkers disclosed the alkylation of terminal olefins with α-aryl aldehydes, utilizing enamine, chiral phosphoric acid, and palladium catalysis with moderate to high levels of enantioselectivity (Figure 1.1.2B).[12] The authors require a rigorous freeze-pump-thaw cycle to achieve modest levels of reactivity and enantioselectivity. More recently, Gong and coworkers disclosed the alkylation of terminal olefins and skipped dienes with pyrazol-5-ones

using chiral phosphoramidites and chiral phosphoric acids (Fig 1.1.2C).[13] Although exhibiting a broad scope in terms of olefins, this reaction was only demonstrated for pyrazol-5-ones, a motif with limited synthetic utility. There is still an unmet need for the highly selective asymmetric allylic C—H alkylation of synthetically useful motifs, such as β-ketoesters, which can undergo diastereoselective reductive aminations or reductions to form enantioenriched sterically congested β-aminoesters and β-hydroxyesters respectively.[8]

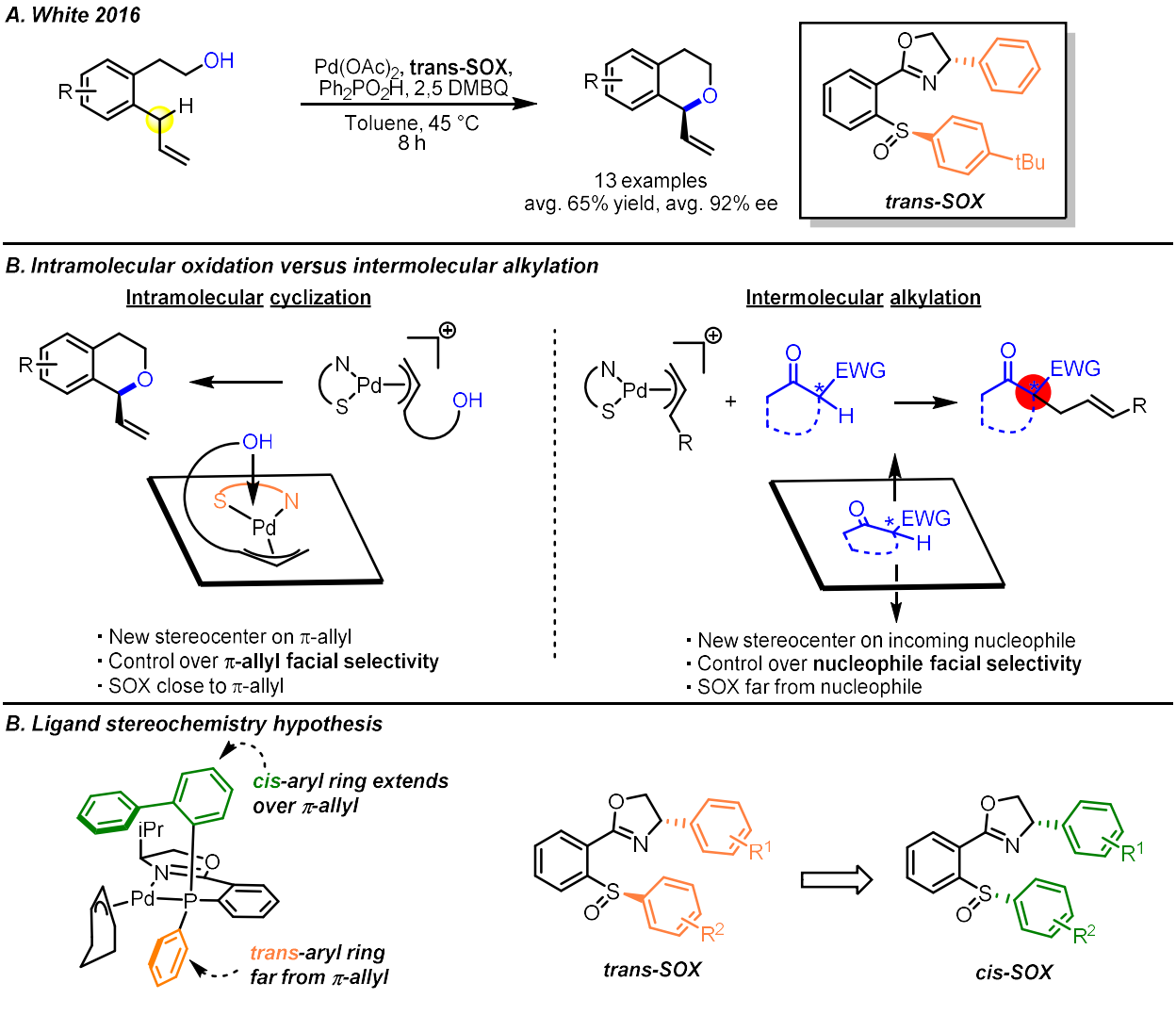
Fig 1.2: Asymmetric Allylic C—H alkylation



The White group has recently reported an Pd/trans-sulfoxide-oxazoline (trans-SOX) complex can catalyze enantioselective cyclizations to form vinyl isochromans from allylic C—H bonds with high levels of enantioinduction (Fig1.1.3A).[14] Notably these catalysts are oxidatively stable, and no effort to exclude air or moisture was taken. It was hypothesized that this could be extended to the more challenging intermolecular asymmetric allylic C—H alkylation. In this case, the asymmetric induction is governed by the facial selectivity of the incoming nucleophile, in which is far away from the chiral Pd center (Fig 1.1.3B). Previous studies of the structurally related phosphinooxazline (PHOX) ligands in asymmetric allylic substitution have shown that differentially substituted phosphine ligands had different effects of asymmetric induction.[15] Specifically, placing steric bulk cis to the oxazoline substituent had a stronger effect on the enantioinduction in comparison to bulky substituents trans to the oxazoline. Potentially this change can be extended to the SOX ligand, where the diastereomer of the trans-SOX, cis-SOX, could have a stronger effect on enantioinduction.

Herein is disclosed efforts to synthesize sterically congested carbon stereocenters using Pd(II)/cis-SOX catalysis. Initial efforts began with synthetically versatile a-nitrotetralones, to afford masked amino ketones and amino alcohols.[16] This reactivity was then extended to more challenging b-ketoesters to form enantioenriched quaternary carbon stereocenters.[17] Ligand studies revealed a beneficial C—H p interaction which was exploited to increase enantioinduction to synthetically useful amounts.

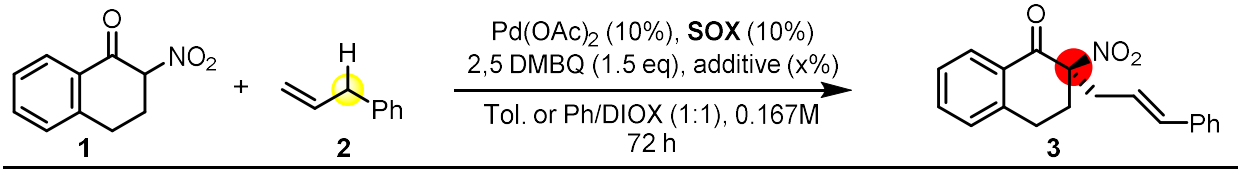
Fig 1.3: Pd(II)/SOX catalyzed asymmetric allylic C—H functionalization



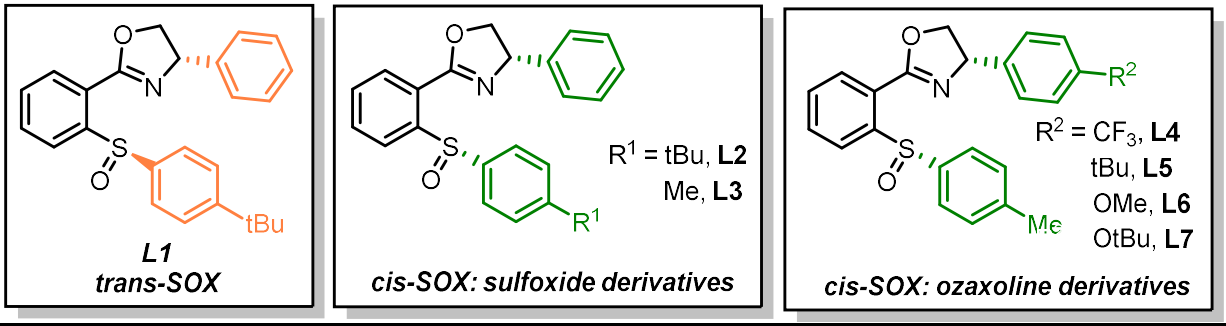
1.2 Results

1.2.1 α-nitrotetralones

Table 1.1: Optimization of α-nitrotetralones



Entry	SOX	$Zn(OAc)_2$ $2H_2O$ (x mol%)	T (^oC)	Yield (%)[a]	ee (%)[b]
1[c]	**L1**	0%	45	65	-20
2[c]	**L2**	0%	45	78	64
3[c]	**L3**	0%	45	80	66
4	**L3**	100%	45	82	79
5	**L3**	100%	5	70	88
6	**L4**	100%	5	78	87
7	**L5**	100%	5	77	90
8	**L6**	100%	5	74	89
9	**L7**	100%	5	81	92
10	**L7**	50%	5	83	92
11	**L7**	25%	5	79	92
12[d]	**L7**	25%	5	60	91



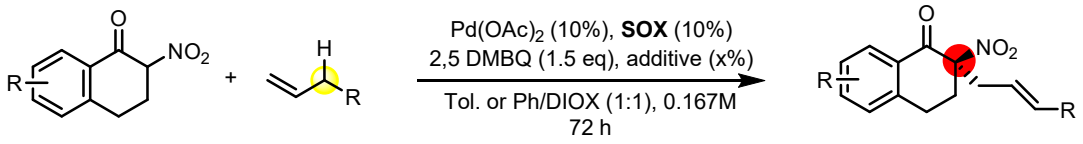
Reaction conditions: Nuc **1** (0.2 mmol), olefin **2** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in benzene/dioxane (0.17 M) at 45 °C for 24 h or at 5 °C for 72 h. Pd and ligand were pre-stirred in benzene at 45 °C for 10 min. a) Isolated yields. b) Determined by chiral HPLC. c) In toluene. d) 1 equiv of Nuc 1.

Optimization began by exploring the asymmetric allylic C—H alkylation of α-nitrotetralone (**1**) with allyl benzene (**2**) catalyzed by Pd(OAc)2, SOX ligand **L1** and 2,5 DMBQ as the stochiometric oxidant. Under the previous optimal conditions for asymmetric allylic C—H oxidations, the coupled product **3** was formed in 65% yield with -20% ee (Entry 1).[14] Consistent

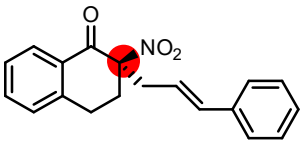
with the ligand stereoselectivity hypothesis, switching to **L2**, the diastereomer of **L1**, the enantioinduction increased to 64% ee while maintaining synthetically useful yields (Entry 2). Switching the 4-substituent from a tBu to a Me group had a moderate increase in yield and enantioinduction (Entry 3, 80% yield, 66% ee). The 4-methyl substituted sulfoxide was preferred due to its relative ease of synthesis. Basic additives are used in traditional allylic functionalizations, and the identity of the counterion can change the level of enantioinduction. A quick examination of acetate additives (not shown) revealed 100 mol% $Zn(OAc)_2$ as an additive can provide a modest increase in enantioinduction using a mixture of benzene and dioxane as the solvent (79% ee, Entry 4). The temperature can be decreased from 45 °C to 5 °C to further increase the enantioinduction (88% ee, Entry 5).

Modifications to the aryl oxazoline were next examined. Substituting the 4-position of the oxazoline aryl ring with an electron withdrawing CF_3 group showed a slight decrease in asymmetric induction (**L4**, 87% ee, Entry 6). In contrast, electron donating tBu (**L5**) and OMe (**L6**) groups slightly increased the enantioinduction to synthetically useful levels (Entries 7 and 8). Combining these led to **L7**, where an OtBu group was in the 4-position of the oxazoline aryl ring. **L7** gave the optimized result with 81% yield and 92% ee (Entry 9). The amount of added Zn(OAc)2 could be decreased with only a slight decrease in the yield (Entries 10 and 11). Finally, the equivalents of nucleophile can be reduced from 2 equivalents to 1 equivalent while maintaining high levels of enantioinduction and only a moderate drop in yield (Entry 12).

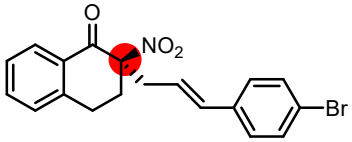
Table 1.2: α-nitrotetralone scope



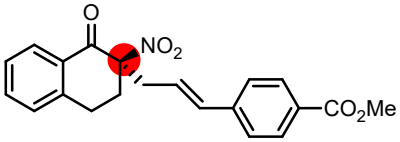
Electrophiles



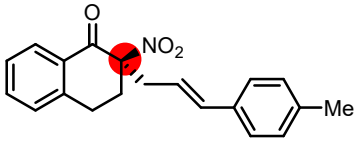
4
81% yield
92% ee



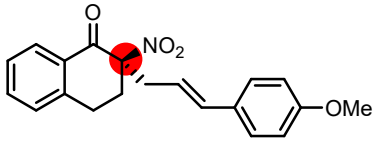
5
66% yield
92% ee



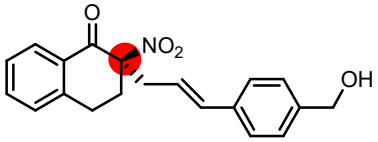
6
68% yield
90% ee



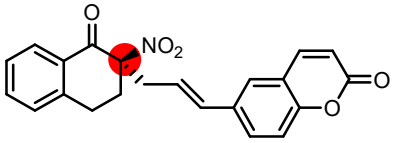
7
60% yield
92% ee



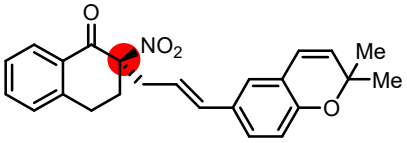
8
51% yield[a]
92% ee



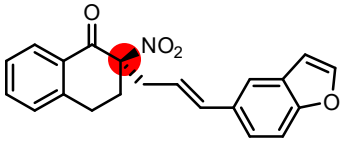
9
65% yield
90% ee



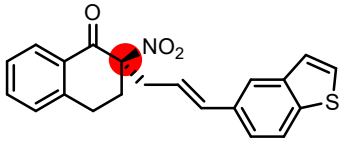
10
65% yield
90% ee



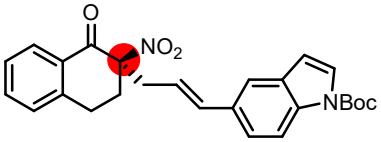
11
65% yield
93% ee



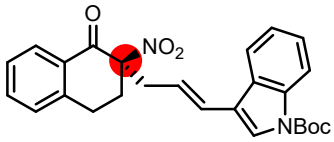
12
64% yield
92% ee



13
57% yield
92% ee

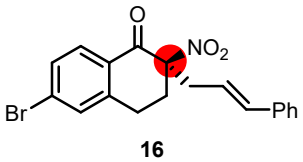


14
63% yield
93% ee

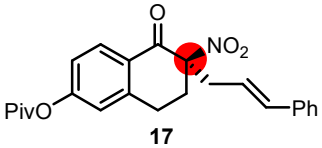


15
54% yield
91% ee

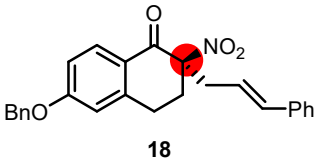
Nucleophiles



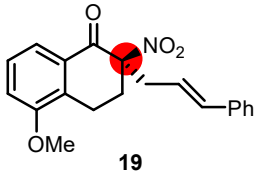
16
64% yield
90% ee



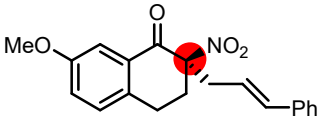
17
58% yield
93% ee



18
48% yield
88% ee



19
67% yield
90% ee



20
58% yield
92% ee

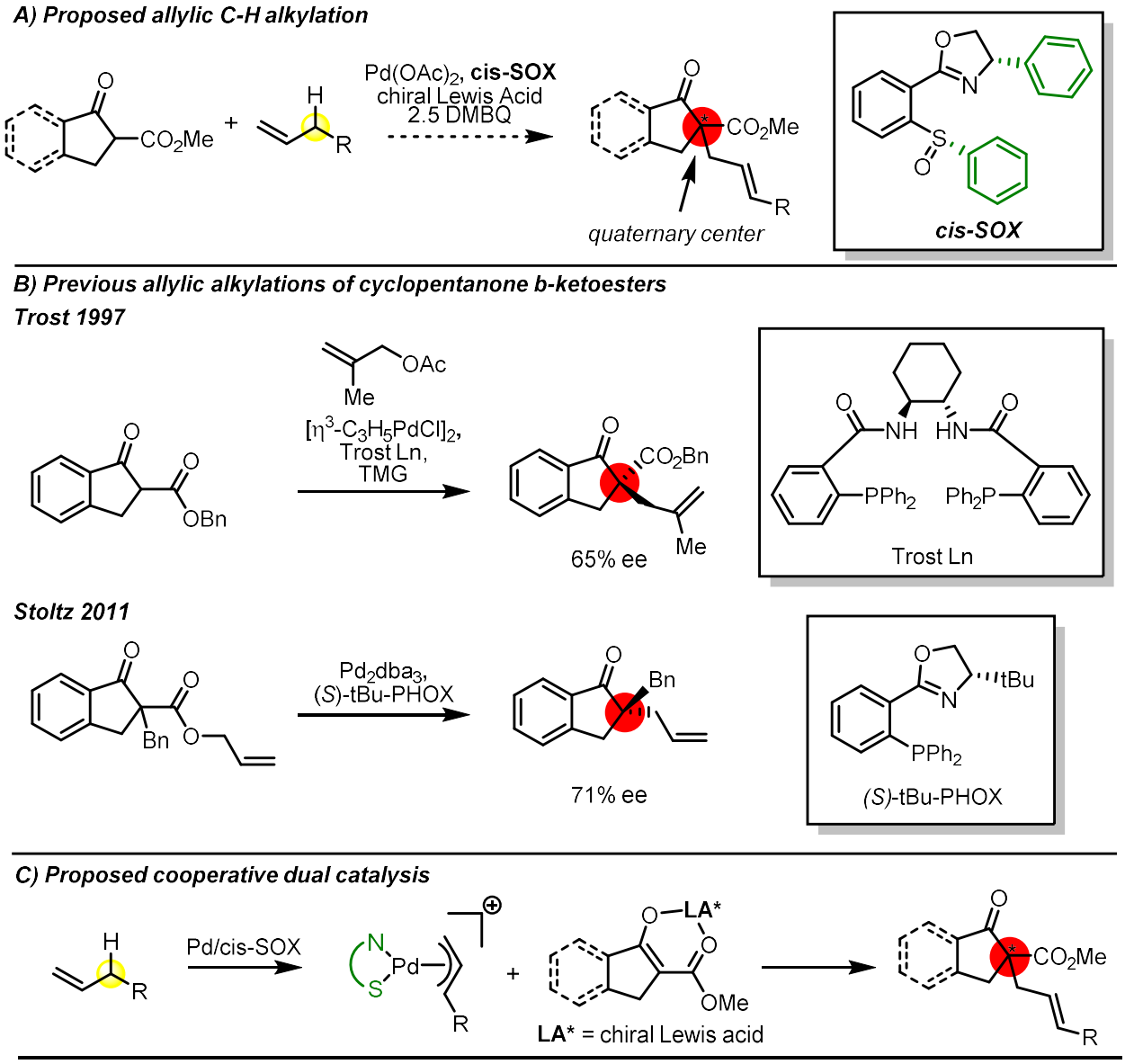
Reaction conditions: Nuc **1** (0.2 mmol), olefin **2** (0.1 mmol), Pd(OAc)2 (0.01 mmol), **L7** (0.01 mmol), 2,6-DMBQ (0.15 mmol) in benzene/dioxane (0.17 M) at 5 °C for 72 h. Pd and ligand were pre-stirred in benzene at 45 °C for 10 min. a) **L5** used.

With the optimized conditions the allyl arene scope was next explored (Table 1.2.1.2). A variety of electron-neutral and electron-poor allyl benzene derivatives were coupled to α-nitrotetralone in synthetically useful yields with high enantioselectivities (**4—7**). Notably, previous allylic C—H alkylations could not functionalize electron rich allyl arenes,[10,11] however this Pd/SOX catalysis was able to functionalize allyl anisole in moderate yield with excellent levels of asymmetric induction (**8**, 51% yield, 92% ee). In addition, a free alcohol which could potentially bind the Pd-center was well tolerated (**9**). A series of biologically relevant hetereocycles, including coumarin, chromene, benzofuran, benzothiophene, and 3- or 5-substituted boc-indoles all coupled smoothly in moderate yields and high enantioselectivities (**10—15**). Of note, the benzothiophene substrate (**13**) which has a sulfur which could bind to the Pd-center, provided one of the highest levels of asymmetric induction in the table.

Several derivatives of the tetralone core were next examined. Previous allylic C—H alkylations showed poor nucleophile diversity, specifically with tetralone derivatives.[10,11] Electron poor bromine and pivalate substituents in the 6 position were well tolerated, and only a slight decrease in enantioinduction was observed with the electron rich benzyloxy substitution in the same position (**16—18**). Oxygen substitution could be moved to the 5 or 7 positions while maintaining synthetically useful enantioselectivities (**19—20**). A crystal structure of product **20** was used to determine the absolute stereochemistry of the α-nitrotetralone products.

1.2.2. Efforts to increase asymmetric induction in β-ketoesters through cooperative dual catalysis

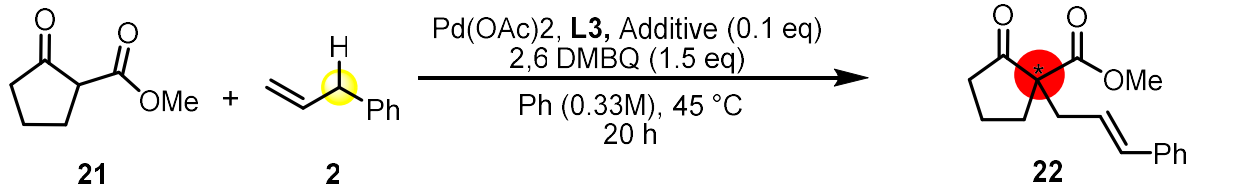
Fig 1.4: Asymmetric allylic alkylation with cyclopentanone β-ketoesters



In the previous section, Pd(II)/cisSOX catalysis was shown to catalyze allylic C—H alkylations of α-nitrotetralone nucleophiles (Chapter 1.2.1), and it was hypothesized this reactivity could be extended to the more challenging cyclic β-ketoesters. Such a transformation would afford enantiomerically enriched quaternary centers. Traditional allylic alkylations *via* allylic substitutions with small cyclic cyclopentanone based nucleophiles formed new quaternary centers

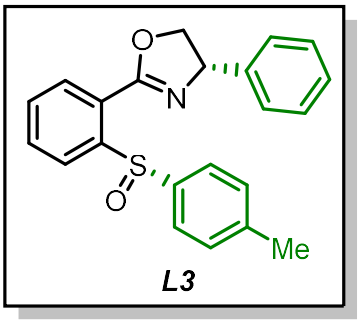
in moderate enantioselectivities, potentially due to the small size and increased flexibility of the β-ketoester nucleophile (Figure 1.2.2.1B).[17] Potentially the addition of a Lewis acid could increase the rigidity of the prochiral nucleophile, increasing enantioinduction. In addition, a chiral Lewis acid could be appended to the nucleophile, potentially serving as a handle to increase enantioselectivity through cooperative dual catalysis, in which a chiral palladium π-allyl could be matched with a chiral Lewis acid/β-ketoester complex. Such cooperative dual catalytic systems have been demonstrated previously with Pd-π-allyl chemistry.[19]

Table 1.3: Initial investigations into Lewis acid additives



21 **2** **22**

Entry	Additive	Yield (%)[a]	ee (%)[b]
1	None	24%	-20%
2	$Cu(OAc)_2$	29%	-25%
3	$Cu(OTf)_2$	36%	8%
4[c]	$Bu_4N(OAc)$	34%	-19%



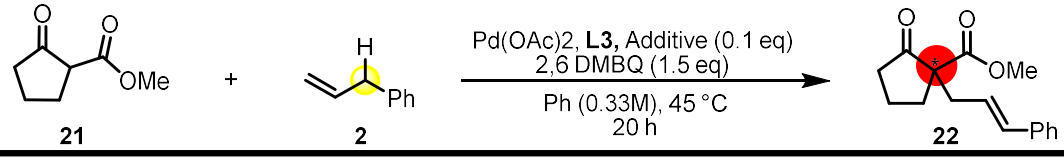
L3

Reaction conditions: Nuc **21** (0.2 mmol), olefin **2** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in benzene (0.33 M) at 45 °C for 20 h. Pd and ligand were pre-stirred in benzene at rt for 10 min, and nucleophile and additive were prestirred for the same amount of time in a sperate vial a) NMR yield. b) Determined by chiral HPLC. c) 0.2 equivalents of additive used.

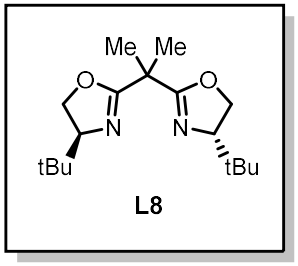
The study commenced with initial investigations into potential Lewis acid additives into the asymmetric allylic C—H alkylation of methyl 2-oxocyclopentane-1-carboxylate (**21**) with allyl benzene (**2**) catalyzed by $Pd(OAc)_2$ and SOX ligand **L3** (Table 1.2.2.1). With no additives, the coupled product (3) was encouragingly observed in a modest 23% yield with -20% ee (Entry 1). Upon the addition of $Cu(OAc)_2$, we observed a slight increase in the yield and enantioselectivity.

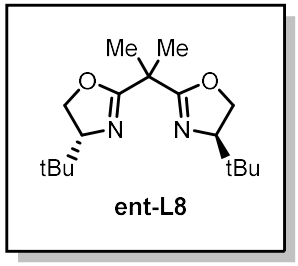
By switching to $Cu(OTf)_2$, we observed an increase in reactivity and an inversion in the "sense" of enantioinduction. Adding exogenous acetate through Bu_4NOAc, did not improve the enantioselectivity, but did increase the yield (Entry 4), suggesting this is an effect of the Lewis acid counterion and not just an increase in the concentration of acetate.

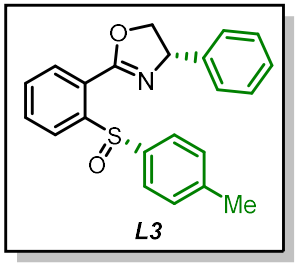
Table 1.4: Investigations into chiral Cu-BOX additives



Entry	Cu(II) salt	Additive	Cu-Add. eq.	Pd-**L1** eq	T (°C)	Yield (%)[a]	ee (%)[b]
1	$Cu(OAc)_2$	**L8**	0.1	0.1	45	26%	-25%
2	$Cu(OTf)_2$	**L8**	0.1	0.1	45	36%	11%
3	[Cu-**L8**]2SbF_6	n/a	0.1	0.1	45	58%	16%
4	[Cu-**ent-L8**]2SbF_6	n/a	0.1	0.1	45	42%	13%
5	[Cu-**ent-L8**]2SbF_6	n/a	0.1	0.05	45	trace	n/a
6	[Cu-**ent-L8**]2SbF_6	n/a	0.1	0.15	45	53%	12%
7	[Cu-**ent-L8**]2SbF_6	n/a	0.05	0.1	45	30%	20%
8	[Cu-**ent-L8**]2SbF_6	n/a	0.01	0.1	45	65%	18%
9[c]	[Cu-**ent-L8**]2SbF_6	n/a	0.1	0.1	45	31%	9%
10	[Cu-**L8**]2SbF_6	n/a	0.1	0.1	RT	trace	n/a
11[d]	[Cu-**L8**]2SbF_6	n/a	0.1	0.1	RT	trace	n/a







Reaction conditions: Nuc **21** (0.2 mmol), olefin **2** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in benzene (0.33 M) at 45 °C for 20 h. Pd and ligand were pre-stirred in benzene at rt for 10 min. and nucleophile and additive were prestirred for the same amount of time in a sperate vial a) NMR yield. b) Determined by chiral HPLC. c) Precomplexed Pd-**L3** isolated and used. d) 72 h reaction time

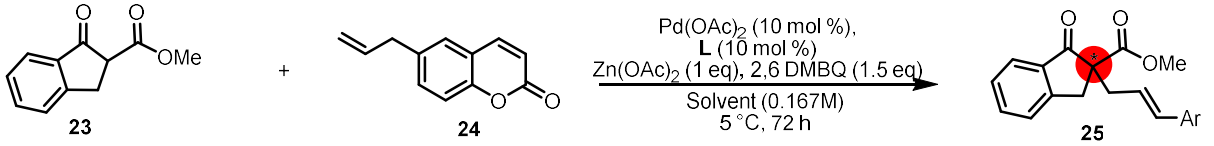
Cu/bis-oxazoline (Cu/BOX) complexes have been known to chelate and activate malonate type nucleophiles.[20] A chiral Cu/**L8** complex could function as a chiral Lewis acid necessary for the nucleophilic coupling partner.[21] The alkylation of methyl 2-oxocyclopentane-1-carboxylate (**21**) and allyl benzene (**2**) was examined over a series of Cu(II) salts with chiral bisoxazoline **L8**. Unexpectedly, the BOX ligand **L8** had little affect when combined with $Cu(OAc)_2$ (Entry 1).

$Cu(OTf)_2$ with **L8** increased the yield (Entry 2) however, only slightly increased the enantioselectivity. With the Cu/**L8**-SbF_6 complex, a dramatic boost in yield was observed (Entry 3). Under the assumption the combination of Cu/**L8** with Pd/**L3** was the "mismatched case," the other enantiomer BOX enantiomer (**ent-L8**) was examined. Unanticipatedly both enantiomers of the Cu/**L8**-SbF_6 system favored the same enantiomer (Entry 4), indicating the Cu/**L8**-SbF_6 could be affecting another step in this mechanism that is not the enantio-determining step.

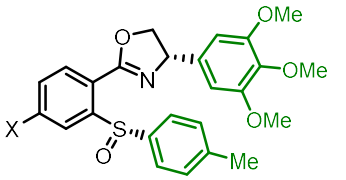
Inspired by the dramatic increase in the yield with added, the amounts of the Pd/**L3** complex and the Cu/**ent-L8** were varied. Although an increase in Cu relative to Pd (1:2 ratio of Pd/**L3** to Cu/**ent**-**L8**-SbF_6 shut the reaction down (Entry 5), an increase in the amount of Pd relative to Cu (1.5:1 ratio of Pd/**L3** to Cu/**ent**-**L8**-SbF_6) restored reactivity (Entry 6). The Cu/**ent**-**L8**-SbF_6 complex could have an inhibitory effect on the reaction and examined conditions with a minimal amount of Cu/**ent**-**L8**-SbF_6 (Entries 7 and 8). Gratifyingly, the yield increased significantly when 1% of Cu/**ent**-**L8**-SbF_6 is used. Complexing the Pd to the SOX ligand showed no improvement (Entry 9). Attempts to increase the enantioselectivity of this reaction by lowering the temperature led to no reactivity (Entries 10,11). Collectively, due to the poor yields and enantioselectivities observed in this system, the smaller β-ketoesters were not pursued further.

1.2.3: Preliminary Investigations into indanone β-ketoesters

Table 1.5: Initial optimization of indanone β-ketoesters



Entry	L	Solvent	Yield (%)[a]	ee (%)[b]
1	**L3**	Ph:Dioxane (1:1)	83%	68%
2	**L7**	Ph:Dioxane (1:1)	64%	71%
3	**L7**	Dioxane	79%	78%
4	**L7**	Ph	47%	55%
5	**L7**	Toluene	20%	52%
6	**L7**	DME	50%	60%
7	**L7**	TBME	n.d	n/a
8[c]	**L7**	Dioxane	18%	50%
9	**L8**	Dioxane	95%	81%

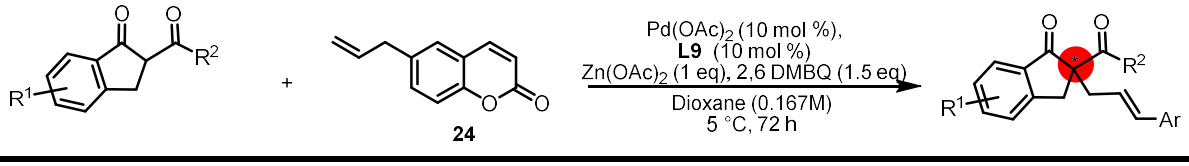


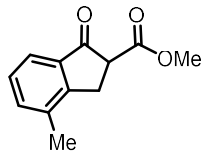
Reaction conditions: Nuc **23** (0.2 mmol), olefin **24** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 20 h. Pd and ligand were pre-stirred in solvent at rt for 10 min a) NMR yield. b) Determined by chiral HPLC. c) no $Zn(OAc)_2$ added.

Several of the issues with the cyclopentanone substrate **21** could potentially be addressed solved by adding a phenyl backbone to the substrate; increasing the steric bulk of the prochiral faces of the nucleophile could increase enantioinduction and increasing the acidity of the α-proton could increase reactivity (Table 1.2.3.1). Utilizing conditions optimized for the previously discussed allylic C—H alkylation of α-nitrotetralones, 2-mehtylester-1-indanone **23** could encouragingly be alkylated with 6-allylcoumarin **24** to afford **25** in 83% yield and 68% ee (Entry 1). 6-allylcoumarin was chosen as a screening electrophile due to its ease in purification and identification *via* chiral HPLC. It is worth noting, the cyclopentanone substrate **21** displayed mild reactivity at room temperature, and is unlikely to alkylate at 5 °C. Switching to the bulkier and more electron rich ligand **L7** a small but noticeable increase in enantioinduction was observed (Entry 2). The effect of the solvent was examined next. Switching from a mixture of benzene and dioxane (1:1) to pure dioxane increased the enantioselectivity to (78% ee) (Entry 4). In contrast, in pure benzene the reaction gave diminished yields and enantioselectivities. This diminishment held through for a variety of other aryl and ethereal solvents. including toluene, DME, and TBME

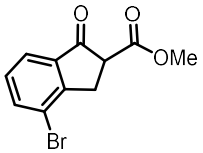
(Entries 5-7). This effect could arise from the chelating ability of dioxane to the Zn^{2+}. When no $Zn(OAc)_2$ is added, we observed a severely diminished yield and significantly lowered enantioinduction, highlighting the necessity for a Lewis acid in this system (Entry 8). Finally, the inclusion of a CF_3 moiety on the backbone increases both the yield and enantioselectivities to near synthetically useful amounts (95% yield, 81% ee, Entry 9)

Table 1.6: Preliminary indanone nucleophile scope

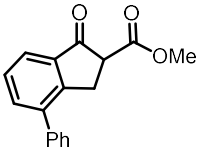




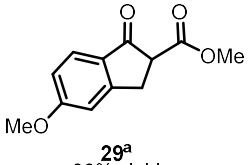
26[a]
81% yield
83% ee



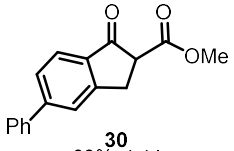
27
24% yield
72% ee



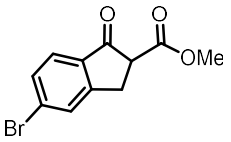
28
41% yield
85% ee



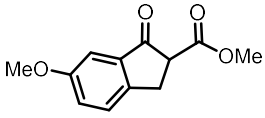
29[a]
96% yield
81% ee



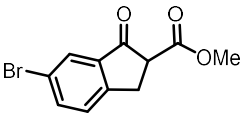
30
63% yield
83% ee



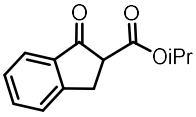
31
10% yield
74% ee



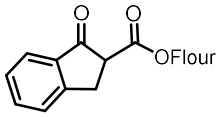
32
80% yield
78% ee



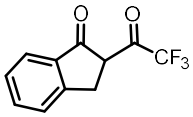
33
n.d.



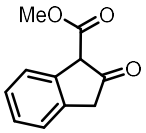
34[a]
71% yield
72% ee



35[a]
20% yield
65% ee



36
n.d.



37
n.d.

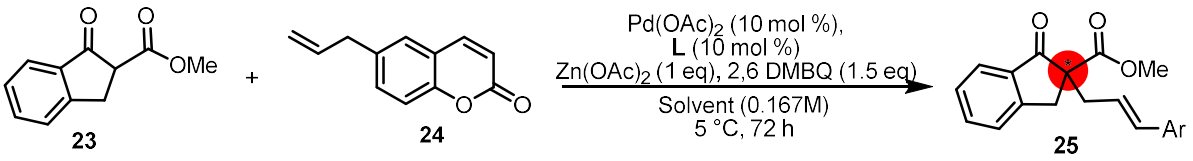
Reaction conditions: Nuc **23** (0.2 mmol), olefin **2** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 20 h. Pd and ligand were pre-stirred in solvent at rt for 10 min a) **L10** used.

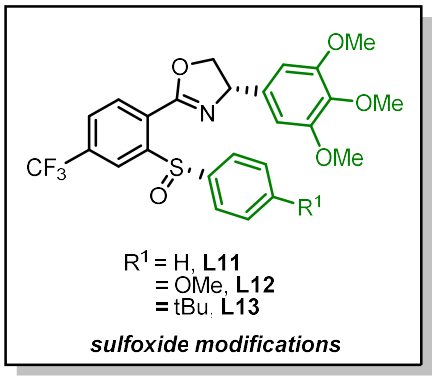
With preliminary conditions established, an initial indanone scope was explored (Table 1.2.3.2). Substitution on 4 position of the ring was tolerated for small groups, such as methyl, but switching to larger and/or more electron withdrawing moieties lowered the yield (**26—28**) albeit with increased enantioselectivity in the case of the 4-phenyl substituent. This substitution will be

discussed more in a following section (see 1.2.5). Substitution at the 5 position was well tolerated, with the electron rich indanone **29** giving 96% yield and 81% ee and the bulky **30**, undergoing alkylation in 63% yield and 83% ee. Unfortunately, when this position was substituted with a bromide, the yields and enantioselectivities diminished (**31**). An electron rich substituent 6 position (**32**) worked in synthetically useful yields and decent enantioselectivities but observed no reactivity with the analogous electron poor substrate (**33**). Finally, different esters were competent in this reaction, albeit lower enantioselectivities (**34**, **35**) however the more acidic diketone (**36**) and the isomer 1-methylester-2-indanone (**37**) were not.

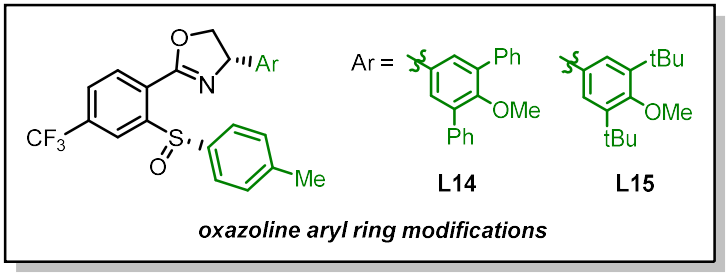
1.2.4: Development of optimal ligand for indanone b-ketoesters

Table 1.7: Indanone β-ketoester ligand screening





Entry	Ln	Yield (%)[a]	ee (%)[b]
1	**L11**	85%	79%
2	**L12**	86%	79%
3	**L13**	77%	81%
4	**L14**	67%	53%
5	**L15**	38%	47%

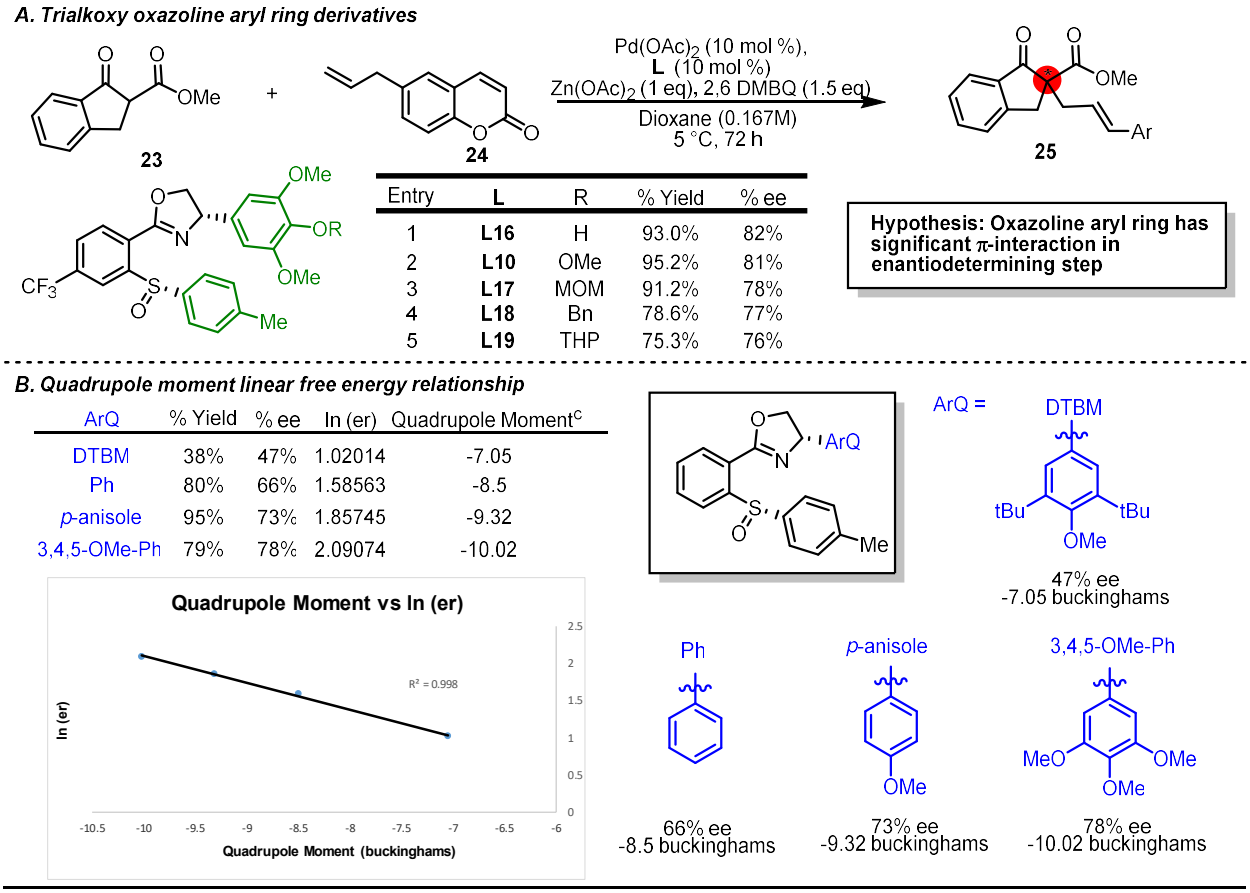


Reaction conditions: Nuc **23** (0.2 mmol), olefin **24** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 20 h. Pd and ligand were pre-stirred in solvent at rt for 10 min a) NMR yield. b) Determined by chiral HPLC. c) no $Zn(OAc)_2$ added.

With preliminary results established for the indanone β-ketoester, a deeper analysis of ligand substituents was undertaken to determine key ligand features that contribute to enantioselectivity and design new SOX ligands to increase level of enantioinduction for this system (Table 1.2.4.1). The sulfoxide aryl unit was first analyzed. Moving to the phenyl sulfoxide **L11** or more electron rich OMe substituent **L12** had little effect on the enantioinduction or yield (Entries 1 and 2). The larger 4-tBu phenyl sulfoxide **L13** had increased the enantioinduction by a modest but appreciable amount (81%, Entry 3). Re-examining the oxazoline moiety, the increase in asymmetric induction from the trimethoxy ligand **L9** could be from either the steric bulk of that trimethoxy aryl ligand, or from the electron rich nature of that aromatic ring. Ligands **L14** and

L15, both of which are significantly bulkier than the trimethoxy moiety of **L9**. Both the 3,5 diphenyl and 3,5 di-tertbutyl modifications had and overall detrimental effect to the system, affording the alkylated product in 53% and 47% ee respectively (Entries 4 and 5). This suggests the increase in enantioinduction gained from the trimethoxy aryl ring of **L9** and **L10** is an electronic effect.

Fig 1.5: Determining a beneficial π-interaction

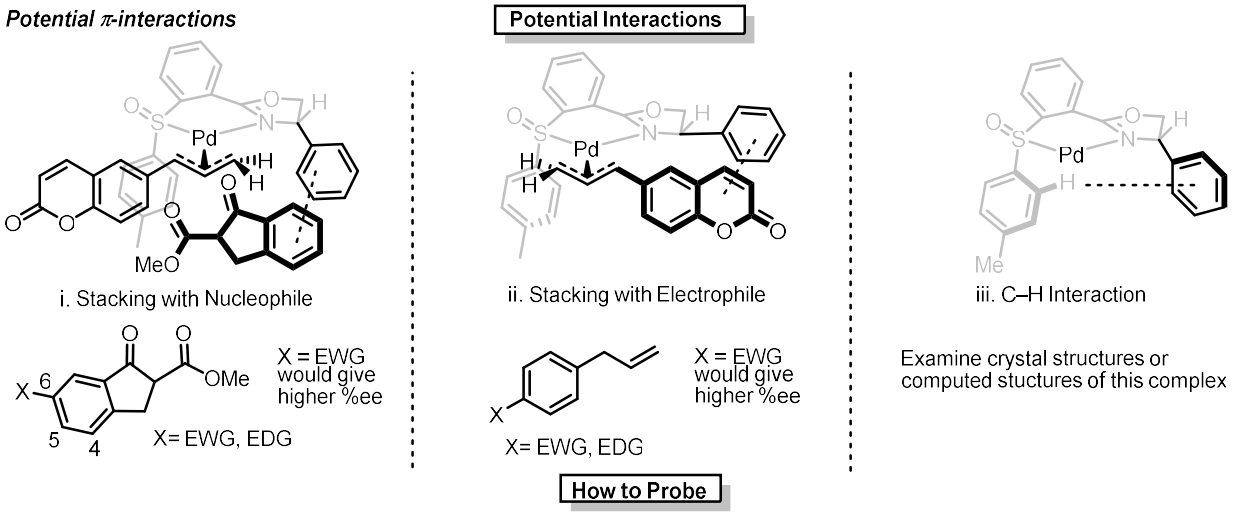


Reaction conditions: Nuc **23** (0.2 mmol), olefin **24** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 20 h. Pd and ligand were pre-stirred in solvent at rt for 10 min a) NMR yield. b) Determined by chiral HPLC. c) Calculated with Gaussian using 6-31G(d,p) basis set and RHF level of theory

In order to understand the nature of this electronic effect, and better understand the detrimental nature of steric bulk around the oxazoline aryl ring, a series of trialkoxy oxazoline aryl rings were examined where the methyl group on the 4-position of the oxazoline aryl ring of **L10** was exchanged for a variety of alkoxy substituents (Fig 1.2.4.1A). As the steric bulk of that

position increased, a small but significant decrease in the level of enantioinduction is observed. Potentially, this aryl ring has a beneficial π-interaction in the enantio-determining step, and adding steric bulk at that position interrupts this interaction.[22] Such π-interactions have been cited as key elements in various reactions, including the Sharpless asymmetric dihydroxylation[23] and Jacobsen's cationic polyene cyclization.[24] In addition, theoretical studies implicate ligand-substrate secondary intermolecular interactions as critical elements of regioselective allylic functionalization.[25] To test this hypothesis, the relationship between the enantiomeric ratio and the quadrupole moment[26] of the oxazoline's aryl ring was examined (Figure 1.2.4.1B). Quadrupole moments are often implicated in π-interactions,[27,28] and have been used as a descriptor for cation-π binding in Jacobsen's cationic polyene cyclization.[24] Examining several ligands with a regular distribution of quadrupole moments,[26,29,30] a linear free energy relationship between the aryl quadrupole moment and the natural logarithm of the enantiomeric ratio was discovered. This suggests a significant π-interaction is present in the enantio-determining step of this reaction.

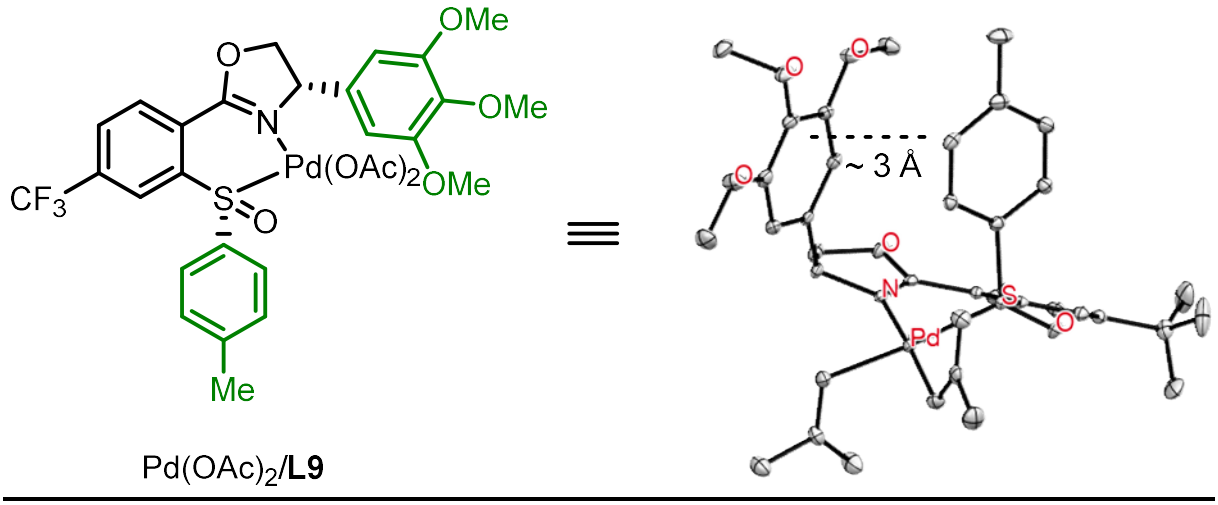
Figure 1.6: Potential π-interactions



Three potential π-interactions were examined as contributors for this increase in enantioselectivity (Fig 1.2.4.2). The oxazoline aryl ring could have a π-π interaction with either

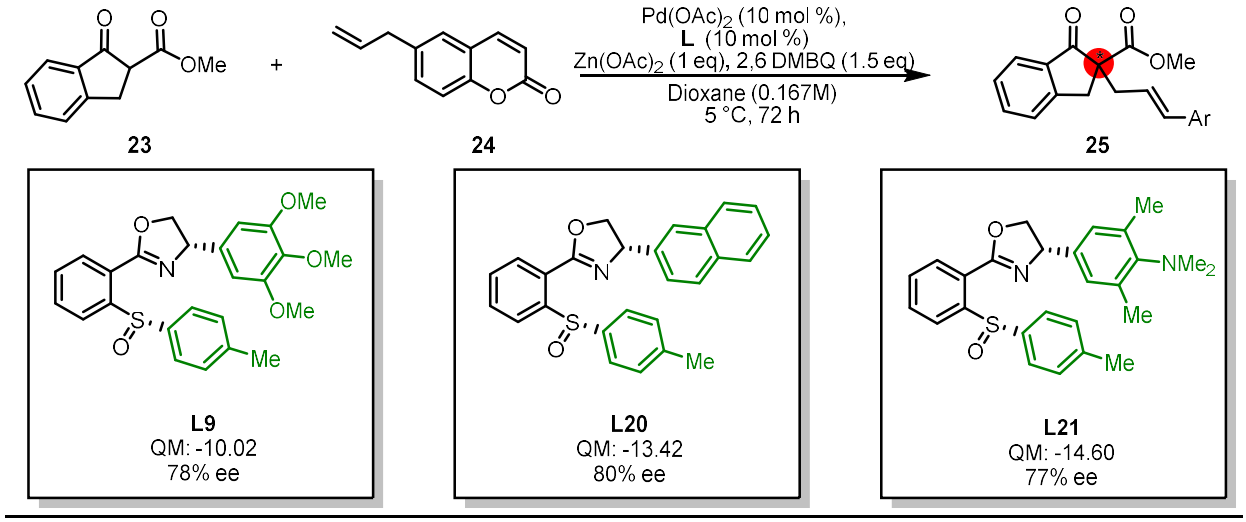
the aryl ring of the nucleophile or the aryl ring of the electrophile. Due to the interconversion of π-allyl isomers observed for terminal olefins,[15] these two scenarios were deemed unlikely. In addition, electron withdrawing groups on the indanone core gave lower levels of enantioinduction compared to electron rich or neutral modifications. The last scenario involves a C—H π-interaction between a C—H bond on the sulfoxide aryl ring and π-system of the oxazoline aryl ring. Such an interaction could rigidify the fluxional ligand structure and increase the effect of steric bulk on various parts of the complex. To probe this, a crystal structure of Pd(OAc)2/**L10** was obtained. A small but appreciable rotation of the sulfoxide aryl C—H bond towards the oxazoline aryl ring was observed, indicating this may be the beneficial π -interaction.

Figure 1.7: $Pd(OAc)_2$/**L9** crystal structure.



$Pd(OAc)_2$/**L9**

Figure 1.8: Increasing the quadrupole moment of the aryl oxazoline ring

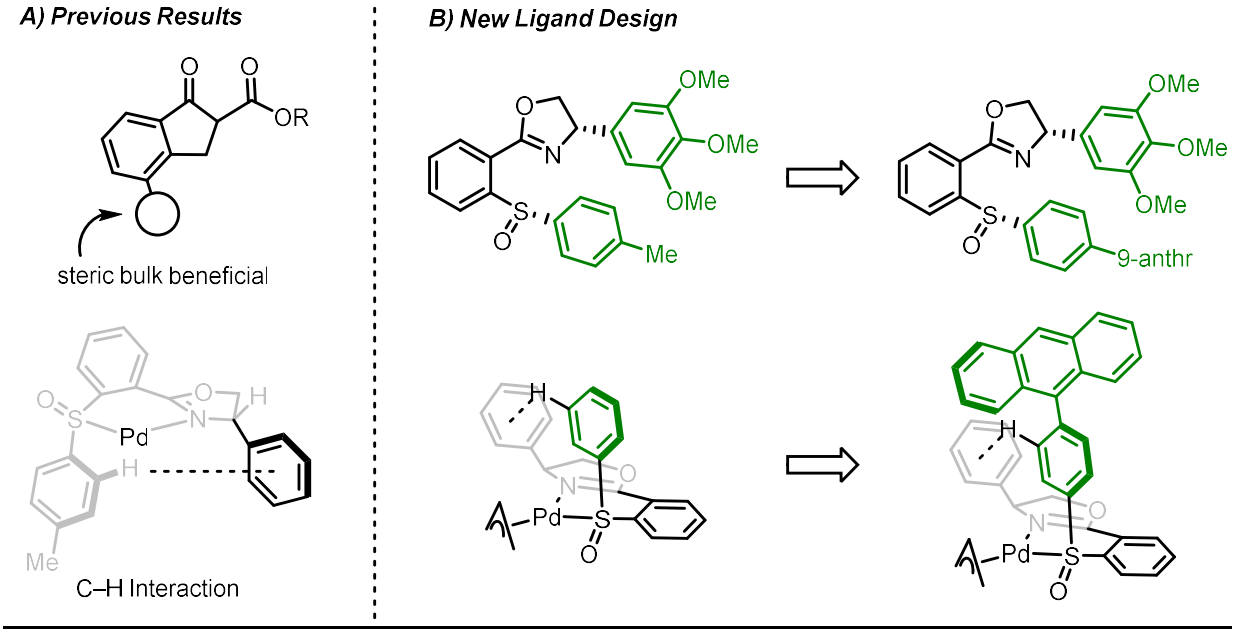


Reaction conditions: Nuc **23** (0.2 mmol), olefin **24** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 20 h. Pd and ligand were pre-stirred in solvent at rt for 10 min %eedDetermined by chiral HPLC. Quadrupole moments are given in buckinghams and calculated with Gaussian using 6-31G(d,p) basis set and RHF level of theory

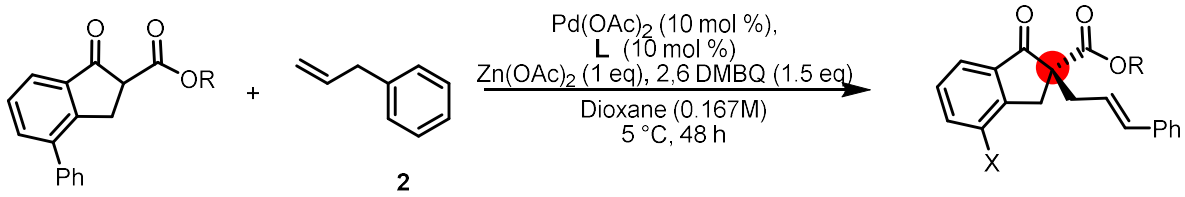
Efforts to increase the enantioinduction through ligand manipulation proved unsuccessful (Fig 1.2.4.4). Ligands with an increased quadrupole often included a larger aryl ring, which has been shown in previous studies to lower useful asymmetric induction (see Table 1.2.4.1). For example, naphthyl substituted **L20** was predicted to give 90% ee based on the trend observed in Fig 1.2.4.1, but only 80% ee was observed. Similarly, **L21** with a significantly higher quadrupole moment afforded the coupled product with similar levels of enantioinduction, presumable due to the significant increase in steric bulk from the dimethylamino substituent. Overall, ligand modifications elucidated a key structural element important to enantioinduction, however efforts to exploit this enantioinduction through ligand design did not prove fruitful.

1.2.5: 4-phenyl indanone β-ketoesters

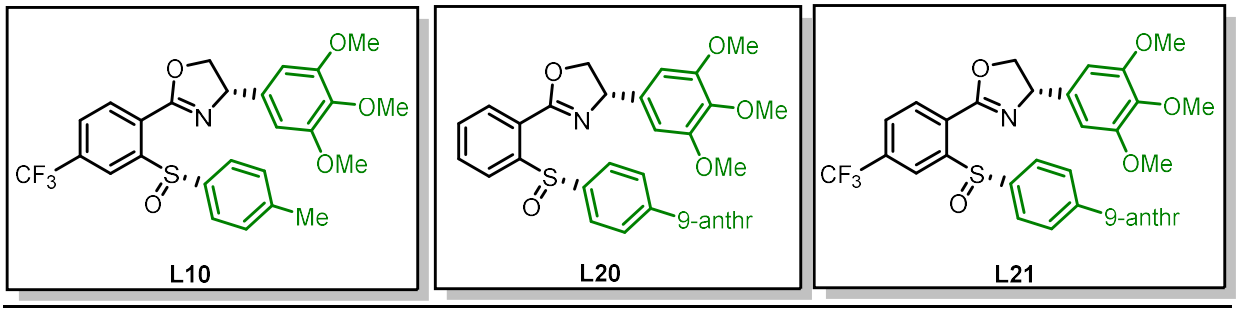
Figure 1.9: Increasing enantioinduction with indanone scaffold



C) 4-Ph-indanone optimization



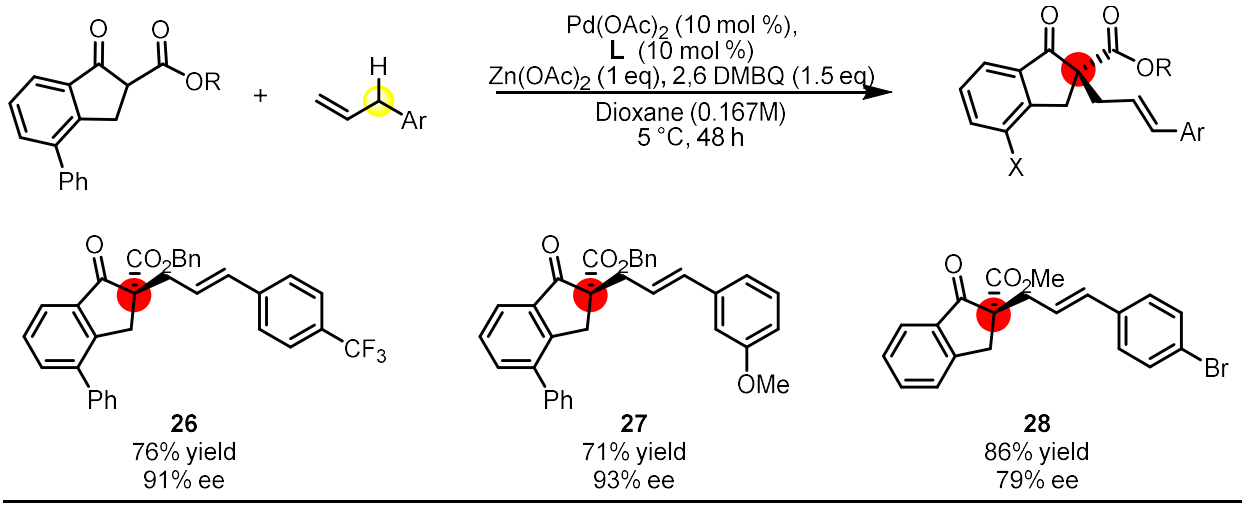
Entry	L	R	% yield[a]	% ee[b]
1	**L10**	Me	41%	85%
2	**L20**	Me	30%	86%
3	**L21**	Me	14%	77%
4	**L10**	Bn	99%	85%
5	**L20**	Bn	40%	90%
6[c]	**L20**	Bn	82%	91%



Reaction conditions: Nuc **23** (0.2 mmol), olefin **24** (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 48 h. Pd and ligand were pre-stirred in solvent at rt for 10 min. a) crude nmr yield. b) determined by chiral HPLC. c) 72h reaction

The previous investigations into the indanone b-ketoester nucleophiles revealed two interesting pieces of data: 4-substitution on the indanone core with a bulky group increased enantioselectivity, and a beneficial C—H π-interaction which could potentially lock the aryl sulfoxide ring in place and increase the effect of steric components on the ligand (Figure 1.2.5.1A). An anthracenyl group at the 4-position of the aryl sulfoxide ring could increase enantioselectivity for these systems. By "locking" the aryl sulfoxide ring in place, a large substituent on the 4-position of the aryl sulfoxide ring could extend over the p-allyl and perhaps have greater enantiocontrol over the oncoming nucleophile (Figure 1.2.5.1B). The asymmetric allylic alkylation of 4-phenyl indanone β-ketoester was used to probe this hypothesis. Potentially, combining the sterically bulky 4-phenyl indanone with the large anthracenyl group would give a combinatorial increase in enantioinduction. Investigation of this hypothesis began with the allylic C—H alkylation of methyl 1-oxo-4-phenyl-2,3-dihydro-1H-indene-2-carboxylate (**28**) with allyl benzene (**2**). With **L10**, the coupled product was observed in 41% yield and 85% ee (Entry 1). By switching to the anthracenyl substituted **L20**, the product was observed in moderately smaller amounts, but encouragingly, in slightly higher levels of asymmetric induction (86% ee, Entry 2). The CF_3 group on this ligand backbone proved to be detrimental in both yield and selectivity (Entry 3). A benzyl group was added to the ester in efforts to lower the pKa of the β-ketoester proton, which did not change the level of enantioinduction, but did provide the product in significantly increased yields (Entry 4). Combining the inclusion of this benzyl ester with the anthracenyl ligand **L20** gave afforded the product in synthetically useful enantioselectivities and yields (Entries 5 and 6).

Table 1.8: 4-phenyl indanone β-ketoester scope



Reaction conditions: Nuc (0.2 mmol), olefin (0.1 mmol), Pd(OAc)2 (0.01 mmol), ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in solvent (0.167 M) at 5 °C for 48 h. Pd and ligand were pre-stirred in solvent at rt for 10 min. % ee determined by chiral HPLC.

With optimal conditions established, a small scope of β-ketoesters couplings were examined (Table 1.2.5.1). Several electron poor allyl arene derivatives were effectively coupled in high yields and high enantioselectivities (**26** and **27**). The highest yield observed when the 4 substitution was removed was 86% yield and 79% ee using an electron poor allyl arene. Notably this work provides stereoselective access to quaternary carbon center.

1.3 Conclusions

In summation, Pd/SOX catalysis enables a highly asymmetric allylic C—H alkylation of a variety of diverse carbon nucleophiles. Critical to this strategy was the cis-SOX ligand, which is thought to have greater control over the approach of the carbon nucleophile. This strategy was used to functionalize a variety of allyl arene terminal olefins with α-nitrotetralone based nucleophiles. Extending this to more challenging β-ketoesters revealed a beneficial π-effect from the ligand. Collectively this work with the research article it is partially adapted from represents the largest variety of nucleophiles used in allylic C—H functionalizations to date.

1.4 Experimental

1.4.1 General Information

All commercially obtained reagents were used as received; $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was stored in a glove box, and weighed out in the air at room temperature prior to use. Benzene and dioxane was purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). 2,6-Dimethylbenzoquinone and zinc acetate dihydrate (reagent grade) were purchased from Sigma-Aldrich and used as received. All allylic C–H alkylation reactions were set up and run under ambient air with no precautions taken to exclude moisture. Reactions at 5ºC were carried out in a cold room, where the temperature is monitored and maintain between 4ºC–6 ºC. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, Cerium-ammonium-molybdate and potassium permanganate stain. Flash chromatography was performed using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.). ^{1}H NMR spectra were recorded on a Varian Unity-u400nb (500 MHz), Varian Inova-500 (500 MHz), or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, sext. = sextet, sept. = septet, o = octet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Carver-Bruker 500 (125MHz) or Varian Unity-500 (125MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$). ^{19}F NMR spectra were recorded on a Varian Unity-500 (470 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$). Chiral high-pressure liquid chromatography (HPLC) analysis was performed on an

Agilent 1100 Series instrument equipped with a UV detector, using a CHIRALPAK AD-RH, OJ-H, IA-3, IB-3, IC-3 column. Optical rotations were measured with a sodium lamp using a 1 mL cell with a 50 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}T^{o}C$ (c = g/100 mL solvent). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof μLtima spectrometer, and electron ionization (EI) and field desorption (FD) spectra were performed on a Micromass 70-VSE spectrometer.

Parts of this work is adapted from the research article "Asymmetric Allylic C–H Alkylation via Palladium(II)/cis-ArSOX Catalysis" (Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. J. Am. Chem. Soc. **2018**, *140*, 10658—10662).

1.4.2: Nitrotetralone Reaction Optimization (Table 1.2.1.1)

Entry 1:

To a ½ dram borosilicate vial with stir bar was added ligand **L1** (4.1 mg, 0.01 mmol, 0.1 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv). Toluene (0.2 mL) was added, and the vial was capped and stirred at 45˚C for 10 mins. Separately, to a ½ dram borosilicate vial with stir bar was added **1** (38.2 mg, 0.20 mmol, 2 equiv), 2,6-dimethylbenzoquinone (20 mg, 0.15 mmol, 1.5 equiv). The catalyst solution was subsequently added to the reaction flask, and toluene (0.4 mL) was used to rinse the catalyst vial, also transferred and added to the reaction flask. Allylbenzene **2** (13.0 μL, 0.10 mmol, 1 equiv) was added. The ½ dram vial was sealed with a Teflon cap, and allowed to stir **for 24 hours** at 45˚C. Afterward, the vial was allowed to cool to RT, followed by the addition of saturated $NaHSO_3$ (aq.) solution (0.2 mL). The mixture was stirred at RT for 15 mins, followed

by the addition of anhydrous $MgSO_4$ and filtration with dichloromethane. The majority of the solvent was removed under reduced pressure, and the remaining mixture was directly subjected to flash column chromatography (2%→5% EtOAc/hexanes) to provide **3** as a light yellow film. Run 1 (20.7 mg, 67% yield, -20% ee); Run 2 (19.4 mg, 63% yield, -20% ee) **Average: 65% Yield, -20% ee.**

Entry 2:

Reaction proceeded according to procedure in Entry 1 using ligand **L2** (4.1 mg, 0.01 mmol, 0.1 equiv). Run 1 (22.7 mg, 74% yield, 64% ee); Run 2 (25.1 mg, 82% yield, 64% ee); **Average: 78% Yield, 64% ee.**

Entry 3:

Reaction proceeded according to procedure in Entry 1 using ligand **L3** (3.7 mg, 0.01 mmol, 0.1 equiv). Run 1 (24.8 mg, 81% yield, 66% ee); Run 2 (24.1 mg, 78% yield, 66% ee); **Average: 80% Yield, 66% ee.**

Entry 4:

To a ½ dram borosilicate vial with stir bar was added ligand **L3** (3.7 mg, 0.01 mmol, 0.1 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv). Benzene (0.2 mL) was added, and the vial was capped and stirred at 45˚C for 10 mins. Separately, to a ½ dram borosilicate vial with stir bar was added **1** (38.2 mg, 0.20 mmol, 2 equiv), 2,6-dimethylbenzoquinone (20 mg, 0.15 mmol, 1.5 equiv) and $Zn(OAc)_2$ dihydrate (22 mg, 0.1 mmol, 1.0 equiv). The catalyst solution was subsequently added to the reaction flask, and benzene (0.1 mL) and dioxane (0.3 mL) was used to rinse the

catalyst vial, also transferred and added to the reaction flask. Allylbenzene **2** (13.0 μL, 0.10 mmol, 1 equiv) was added. The ½ dram vial was sealed with a Teflon cap, and allowed to stir **for 24 hours at 45˚C**. Afterward, the reaction was quenched by the addition of saturated $NaHSO_3$ (aq.) solution (0.2 mL). The mixture was stirred at RT for 15 mins, followed by the addition of anhydrous $MgSO_4$ and filtration with dichloromethane. The majority of the solvent was removed under reduced pressure, and the remaining mixture was directly subjected to flash column chromatography (2%→5% EtOAc/hexanes) to provide **3** as a light yellow film. Run 1 (25.5 mg, 83% yield, 79% ee); Run 2 (24.5 mg, 80% yield, 79% ee); **Average: 82% Yield, 79% ee.**

Entry 5:

General procedure: To a ½ dram borosilicate vial with stir bar was added ligand **L3** (3.7 mg, 0.01 mmol, 0.1 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv). Benzene (0.2 mL) was added, and the vial was capped and stirred at 45˚C for 10 mins. Separately, to a ½ dram borosilicate vial with stir bar was added **1** (38.2 mg, 0.20 mmol, 2 equiv), 2,6-dimethylbenzoquinone (20 mg, 0.15 mmol, 1.5 equiv) and $Zn(OAc)_2$ dihydrate (22 mg, 0.1 mmol, 1.0 equiv). The catalyst solution was subsequently added to the reaction flask, and benzene (0.1 mL) and dioxane (0.3 mL) was used to rinse the catalyst vial, also transferred and added to the reaction flask. Allylbenzene **2** (13.0 μL, 0.10 mmol, 1 equiv) was added. The ½ dram vial was sealed with a Teflon cap, and allowed to stir **for 72 hours at 5˚C**. Afterward, the reaction was quenched by the addition of saturated $NaHSO_3$ (aq.) solution (0.2 mL). The mixture was stirred at RT for 15 mins, followed by the addition of anhydrous $MgSO_4$ and filtration with dichloromethane. The majority of the solvent was removed under reduced pressure, and the remaining mixture was directly subjected to flash column

chromatography (2%→5% EtOAc/hexanes) to provide **3** as a light yellow film. Run 1 (21.8 mg, 71% yield, 88% ee); Run 2 (20.8 mg, 68% yield, 88% ee); **Average: 70% Yield, 88% ee.**

Entry 6:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L4** (4.3 mg, 0.01 mmol, 0.1 equiv). Run 1 (23.3 mg, 76% yield, 87% ee); Run 2 (24.5 mg, 80% yield, 87% ee); **Average: 78% Yield, 87% ee.**

Entry 7:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L5** (4.2 mg, 0.01 mmol, 0.1 equiv). Run 1 (22.7 mg, 74% yield, 90% ee); Run 2 (24.3 mg, 79% yield, 90% ee); **Average: 77% Yield, 90% ee.**

Entry 8:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L6** (3.9 mg, 0.01 mmol, 0.1 equiv). Run 1 (23.8 mg, 77% yield, 89% ee); Run 2 (21.5 mg, 70% yield, 89% ee); **Average: 74% Yield, 89% ee.**

Entry 9:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L7** (4.4 mg, 0.01 mmol, 0.1 equiv). Run 1 (24.0 mg, 78% yield, 92% ee); Run 2 (25.5 mg, 83% yield, 92% ee); **Average: 81% Yield, 92% ee.**

Entry 10:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L7** (4.4 mg, 0.01 mmol, 0.1 equiv) and $Zn(OAc)_2$ dihydrate (**11 mg, 0.05 mmol, 0.5 equiv**). Run 1 (26.2 mg, 85% yield, 92% ee); Run 2 (25.0 mg, 81% yield, 92% ee); **Average: 83% Yield, 92% ee.** (HPLC trace and optical rotation was included for this entry)

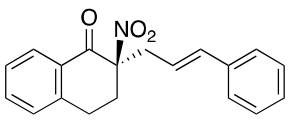
Entry 11:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L7** (4.4 mg, 0.01 mmol, 0.1 equiv) and $Zn(OAc)_2$ dihydrate (**5.5 mg, 0.025 mmol, 0.25 equiv**). Run 1 (25.2 mg, 82% yield, 92% ee); Run 2 (22.9 mg, 75% yield, 92% ee); **Average: 79% Yield, 92% ee.**

Entry 12:

Reaction proceeded according to the General procedure in Entry 5 using ligand **L7** (4.4 mg, 0.01 mmol, 0.1 equiv), nucleophile **1** (19.0 mg, 0.10 mmol, 1 equiv) and $Zn(OAc)_2$ dihydrate (**5.5 mg, 0.025 mmol, 0.25 equiv**). Run 1 (17.1 mg, 56% yield, 91% ee); Run 2 (19.5 mg, 64% yield, 91% ee); **Average: 60% Yield, 91% ee.**

The absolute stereochemistry of alkylated product with nitroketones was assigned based on crystal structure of **3p** (vide infra).

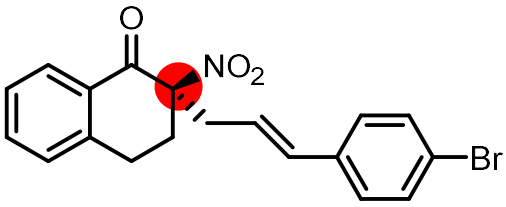


(*R*)-2-cinnamyl-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (**3**): Spectral data matches with previously reported. The enantiomeric excess was determined to be 92% by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min,

55% MeCN in H_2O, λ = 254 nm): t_R(major) = 28.309 min, t_R(minor) = 31.991 min. $[\alpha]^{23}_D$ = +16.2 (c = 1.1, $CHCl_3$).

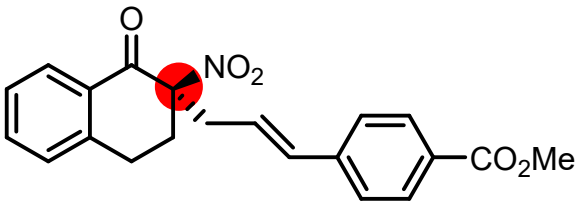
1.4.3: Nitrotetralone Reaction Scope

General procedure for Table 1.2.1.2: To a ½ dram borosilicate vial with stir bar was added ligand **L5** (8.4 mg, 0.02 mmol, 0.1 equiv) or **L7** (8.7 mg, 0.02 mmol, 0.1 equiv) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv). Benzene (0.4 mL) was added, and the vial was capped and stirred at 45˚C for 10 mins. Separately, to a 1 dram borosilicate vial with stir bar was added **1** (76.5 mg, 0.40 mmol, 2 equiv), 2,6-dimethylbenzoquinone (40 mg, 0.3 mmol, 1.5 equiv) and $Zn(OAc)_2$ dihydrate (22 mg, 0.1 mmol, 0.5 equiv). The catalyst solution was subsequently added to the reaction flask, and benzene (0.2 mL) and dioxane (0.6 mL) was used to rinse the catalyst vial, also transferred and added to the reaction flask. Allylarene **2** (0.20 mmol, 1 equiv) was added. The 1 dram vial was sealed with a Teflon cap, and allowed to stir for 72 hours at 5˚C. Afterward, the reaction was diluted with 20 mL EtOAc, which was washed by saturated $NaHSO_3$ (aq.) solution (10 mL) or 5% K_2CO_3 (aq.) solution (10 mL) (*NOTE: The purpose of aqueous wash is for the ease of purification. $NaHSO_3$ was used to remove remaining DMBQ oxidant, whereas K_2CO_3 was used to remove remaining nitroketone nucleophile*). The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the remaining mixture was purified by flash column chromatography to provide product.



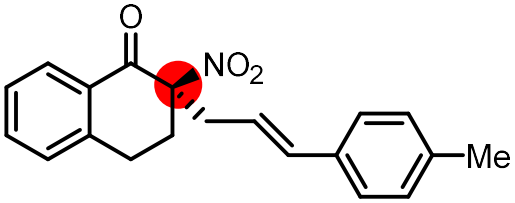
(*R*,*E*)-2-(3-(4-bromophenyl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (5): 4-bromoallylbenzene (39.4 mg, 0.20 mmol, 1 equiv) was

reacted according to the general procedure using **L7** with **$NaHSO_3$ work up**. Purification by flash column chromatography (5%→8% EtOAc/hexanes) provided the product as a white solid. Run 1 (49.5 mg, 64% yield, 92% ee); Run 2 (51.3 mg, 66% yield, 92% ee); Run 3 (52.5 mg, 68% yield, 92% ee). **Average: 66% (±2.0%) yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 60% MeCN in H_2O, λ = 280 nm): t_R(major) = 37.178 min, t_R(minor) = 43.913 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.20 (ddd, *J* = 14.4, 7.2, 1.4 Hz, 1H), 3.15 – 3.06 (m, 2H), 3.05 – 2.91 (m, 2H), 2.47 (ddd, *J* = 14.2, 9.1, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.82, 142.25, 135.34, 134.79, 134.61, 131.70, 130.71, 128.93, 128.83, 127.93, 127.51, 122.56, 121.74, 93.72, 38.12, 31.91, 25.24; HRMS (ESI) m/z calc'd for $C_{19}H_{16}BrNO_3$ [M+Na]+: 408.0211; found 408.0222. $[\alpha]^{23}_D$ = +20.8° (c = 1.43, $CHCl_3$).

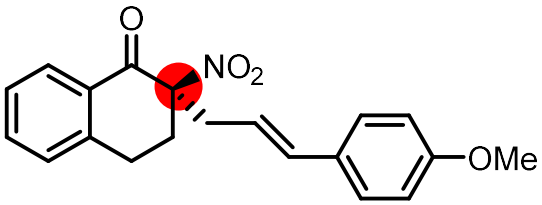


Methyl (*R*,*E*)-4-(3-(2-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)benzoate (6): Methyl 4-allylbenzoate (35.2 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L5** with **K_2CO_3 work up**. Purification by flash column chromatography (8%→10%→15% EtOAc/hexanes) provided the product as a colorless oil. Run 1 (49.2 mg, 67% yield, 90% ee); Run 2 (47.5 mg, 65% yield, 90% ee); Run 3 (52.5 mg, 72% yield, 90% ee). **Average: 68% (±3.5%) yield, 90% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALCEL OJ-H column, 1 mL/min, 40% isopropanol in hexane, λ = 280 nm): t_R(major) = 22.985 min, t_R(minor) = 34.484

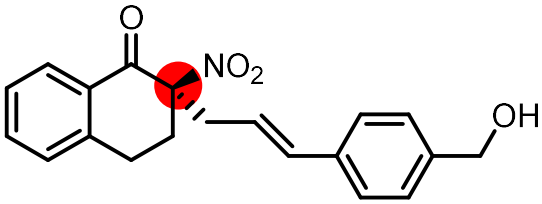
min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.4 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.26 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 6.30 (dt, *J* = 15.4, 7.4 Hz, 1H), 3.90 (s, 3H), 3.24 (dd, *J* = 14.1, 7.1 Hz, 1H), 3.16 – 3.07 (m, 2H), 3.05 – 2.93 (m, 2H), 2.48 (ddd, *J* = 14.3, 9.1, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.76, 166.75, 142.24, 140.77, 135.07, 134.64, 130.68, 129.94, 129.34, 128.94, 128.83, 127.52, 126.30, 124.56, 93.70, 52.11, 38.18, 31.97, 25.24. HRMS (ESI) m/z calc'd for $C_{21}H_{19}NO_5$ [M+H]+: 366.1341; found 366.1331. $[\alpha]^{23}_D$ = +24.8° (c = 0.72, $CHCl_3$).



(*R*,*E*)-2-nitro-2-(3-(*p*-tolyl)allyl)-3,4-dihydronaphthalen-1(2*H*)-one (7): 4-allyltoluene (26.4 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **NaHSO$_3$ work up**. Purification by flash column chromatography (2%→5% EtOAc/hexanes) provided the product as a yellow oil. Run 1 (38.6 mg, 60% yield, 92% ee); Run 2 (36.0 mg, 56% yield, 92% ee); Run 3 (41.4 mg, 64% yield, 92% ee). **Average: 60% (±4.2%) yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 55% MeCN in H_2O, λ = 254 nm): t_R(major) = 43.343 min, t_R(minor) = 46.711 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.12 (dt, *J* = 15.3, 7.4 Hz, 1H), 3.25 (ddd, *J* = 14.5, 7.3, 1.4 Hz, 1H), 3.17 – 3.10 (m, 2H), 3.08 – 2.96 (m, 2H), 2.53 (ddd, *J* = 14.1, 8.9, 4.8 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.97, 142.35, 137.84, 135.89, 134.54, 133.64, 130.72, 129.29, 128.91, 128.83, 127.45, 126.30, 120.50, 93.93, 38.06, 31.66, 25.25, 21.20. HRMS (ESI) m/z calc'd for $C_{20}H_{19}NO_3$ [M+Na]+: 344.1263; found 344.1269. $[\alpha]^{23}_D$ = +6.4° (c = 1.1, $CHCl_3$).

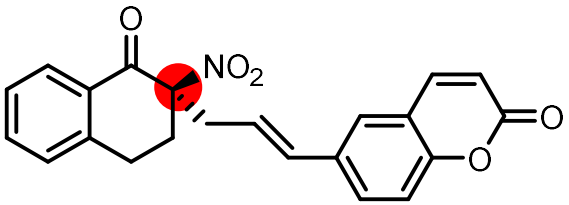


(*R*,*E*)-2-(3-(4-methoxyphenyl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (8): 4-allylanisole (30.0 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L5** with **K_2CO_3 work up**. Purification by flash column chromatography (20%→30%→50% DCM/hexanes) provided the product as a colorless oil. Run 1 (35.4 mg, 53% yield, 90% ee); Run 2 (36.4 mg, 54% yield, 90% ee); Run 3 (31.7 mg, 47% yield, 90% ee). **Average: 51% (±3.7%) yield, 90% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 55% MeCN in H_2O, λ = 254 nm): t_R(major) = 36.912 min, t_R(minor) = 40.779 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.23 (m, 3H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.00 (dt, *J* = 15.3, 7.4 Hz, 1H), 3.80 (s, 3H), 3.20 (ddd, *J* = 14.4, 7.2, 1.3 Hz, 1H), 3.14 – 3.06 (m, 2H), 3.05 – 2.92 (m, 2H), 2.50 (ddd, *J* = 14.1, 8.8, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.00, 159.45, 142.35, 135.42, 134.53, 130.73, 129.24, 128.91, 128.82, 127.60, 127.45, 119.24, 114.00, 93.98, 55.30, 38.09, 31.64, 25.26. HRMS (ESI) m/z calc'd for $C_{20}H_{19}NO_4$ [M+Na]+: 360.1212; found 360.1218. $[\alpha]^{22}_D$ = +7.1° (c = 1, $CHCl_3$).



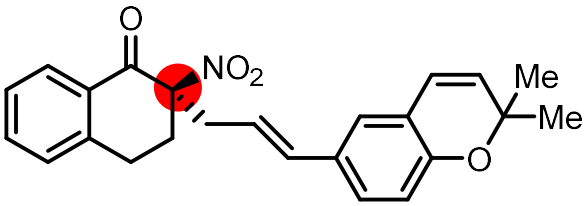
(*R*,*E*)-2-(3-(4-(hydroxymethyl)phenyl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (9): (4-allylphenyl)methanol (30.0 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (15%→20%→30% Acetone/hexanes) provided the product as a colorless oil. Run 1 (41.9 mg, 62% yield, 91% ee); Run 2 (44.3 mg, 66% yield, 91% ee); Run 3

(45.0 mg, 67% yield, 91% ee). **Average: 65% (±2.4%) yield, 91% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALCEL OJ-H column, 1 mL/min, 40% isopropanol in hexane, λ = 260 nm): t_R(major) = 11.964 min, t_R(minor) = 18.490 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.16 (dt, *J* = 15.4, 7.4 Hz, 1H), 4.66 (s, 2H), 3.22 (ddd, *J* = 14.5, 7.2, 1.4 Hz, 1H), 3.15 – 3.07 (m, 2H), 3.06 – 2.93 (m, 2H), 2.49 (ddd, *J* = 14.1, 8.9, 4.7 Hz, 1H), 1.74 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.94, 142.32, 140.62, 135.85, 135.61, 134.59, 130.70, 128.93, 128.83, 127.48, 127.22, 126.59, 121.70, 93.88, 65.02, 38.09, 31.77, 25.25. HRMS (ESI) m/z calc'd for $C_{20}H_{19}NO_4$ [M+Na]+: 360.1212; found 360.1213. $[\alpha]^{23}_D$ = +14.7° (c = 1.6, $CHCl_3$).

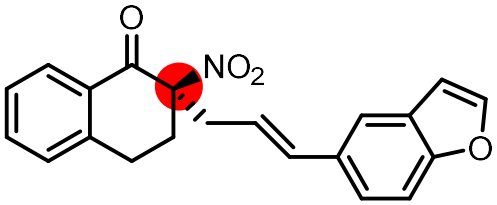


(*R*,*E*)-6-(3-(2-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)-2*H*-chromen-2-one (10): 6-allyl-2H-chromen-2-one (37.2 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (15%→35% EtOAc/hexanes) provided the product as a white solid. Run 1 (47.8 mg, 64% yield, 90% ee); Run 2 (50.5 mg, 67% yield, 90% ee); Run 3 (47.2 mg, 63% yield, 90% ee). **Average: 65% (±2.3%) yield, 90% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 50% isopropanol in hexanes, λ = 254 nm): t_R(major) = 21.454 min, t_R(minor) = 32.135 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 9.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.61 – 6.53 (d, *J* = 15.8 Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H), 6.21 (dt, *J* =

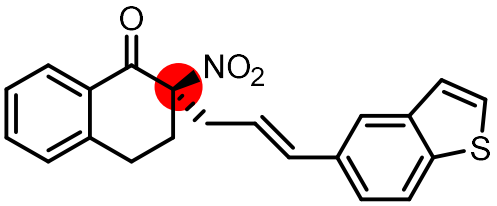
15.8, 7.4 Hz, 1H), 3.23 (ddd, *J* = 14.3, 7.2, 1.4 Hz, 1H), 3.17 – 3.08 (m, 2H), 3.07 – 2.95 (m, 2H), 2.48 (ddd, *J* = 14.3, 9.3, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.80, 160.52, 153.55, 143.21, 142.20, 134.66, 134.01, 133.07, 130.73, 129.76, 128.94, 128.82, 127.54, 125.40, 122.95, 118.87, 117.14, 117.11, 93.73, 38.20, 32.12, 25.25; HRMS (ESI) *m/z* calculated for $C_{22}H_{17}NO_5$ $[M+H]^+$: 376.1185, found 376.1176. $[\alpha]^{22}_D = +30.6^\circ$ (c = 0.81, $CHCl_3$).



(*R*,*E*)-2-(3-(2,2-dimethyl-2*H*-chromen-6-yl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (11): 6-allyl-2,2-dimethyl-2H-chromene (40.0 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (2%→5% EtOAc/hexanes) provided the product as a yellow oil. Run 1 (49.8 mg, 64% yield, 93% ee); Run 2 (52.7 mg, 68% yield, 93% ee); Run 3 (49.1 mg, 63% yield, 93% ee). **Average: 65% (±2.5%) yield, 93% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 65% MeCN in H_2O, λ = 254 nm): t_R(major) = 23.538 min, t_R(minor) = 29.110 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.29 (d, *J* = 9.9 Hz, 1H), 5.97 (dt, *J* = 15.7, 7.5 Hz, 1H), 5.62 (d, *J* = 9.8 Hz, 1H), 3.19 (ddd, *J* = 14.3, 7.3, 1.3 Hz, 1H), 3.15 – 2.92 (m, 4H), 2.49 (ddd, *J* = 14.1, 8.9, 4.8 Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.00, 152.94, 142.35, 135.47, 134.52, 131.19, 130.73, 129.26, 128.90, 128.82, 127.44, 127.35, 124.07, 122.05, 121.23, 119.06, 116.40, 93.98, 76.50, 38.08, 31.65, 28.01, 25.26 ; HRMS (EI) *m/z* calculated for $C_{24}H_{23}NO_4$ $[M]^+$: 389.16271, found 389.16269. $[\alpha]^{22}_D = +2.8^\circ$ (c = 1.26, $CHCl_3$).

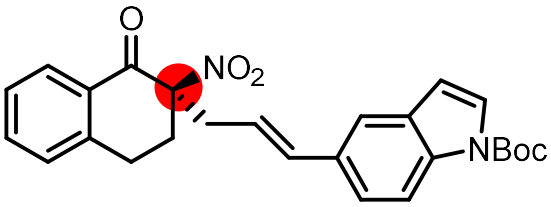


(*R*,*E*)-2-(3-(benzofuran-5-yl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (12): 5-allylbenzofuran (32.0 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (2%→8% EtOAc/hexanes) provided the product as a yellow oil. Run 1 (38.2 mg, 55% yield, 92% ee); Run 2 (48.8 mg, 70% yield, 92% ee); Run 3 (46.1 mg, 66% yield, 92% ee). **Average: 64% (±7.9%) yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 40% isopropanol in hexanes, λ = 254 nm): t_R(major) = 17.595 min, t_R(minor) = 28.628 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.13 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.24 (ddd, *J* = 14.3, 7.2, 1.4 Hz, 1H), 3.16 – 3.07 (m, 2H), 3.06 – 2.95 (m, 2H), 2.55 – 2.47 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.00, 154.75, 145.61, 142.35, 136.13, 134.56, 131.58, 130.73, 128.93, 128.82, 127.78, 127.46, 122.89, 120.43, 119.16, 111.44, 106.64, 93.98, 38.11, 31.73, 25.27; HRMS (ESI) *m/z* calculated for $C_{21}H_{17}NO_4$ $[M+Na]^+$: 370.1055, found 370.1065. $[\alpha]^{22}_D$ = +26.8° (c = 1.33, $CHCl_3$).



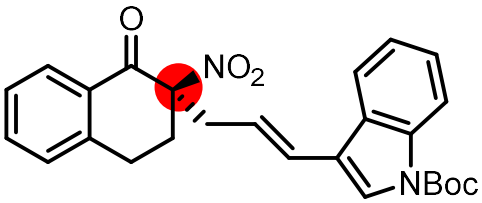
(*R*,*E*)-2-(3-(benzo[*b*]thiophen-5-yl)allyl)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (13): 5-allylbenzothiophene (35.0 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (2%→8% EtOAc/hexanes) provided the product as a white solid. Run 1 (41.3 mg, 57% yield, 92% ee); Run 2 (42.8 mg, 59% yield, 92% ee); Run 3 (41.2 mg, 57% yield,

92% ee). **Average: 57% yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 65% MeCN in H_2O, λ = 254 nm): t_R(major) = 31.236 min, t_R(minor) = 38.111 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 5.5 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.30 (d, *J* = 5.5 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 15.7 Hz, 1H), 6.22 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.26 (ddd, *J* = 14.2, 7.2, 1.3 Hz, 1H), 3.15 (ddd, *J* = 14.3, 7.6, 1.3 Hz, 1H), 3.12 – 3.08 (m, 1H), 3.05 – 2.96 (m, 2H), 2.57 – 2.47 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.95, 142.32, 139.96, 139.23, 136.07, 134.56, 132.85, 130.74, 128.92, 128.85, 127.48, 127.09, 123.87, 122.54, 122.43, 121.73, 121.24, 93.91, 38.18, 31.79, 25.27; HRMS (ESI) *m/z* calculated for $C_{21}H_{17}NO_3S$ $[M+H]^+$: 364.0983, found 364.0997. $[\alpha]^{22}_D$: +9.4° (c = 1.04, $CHCl_3$).

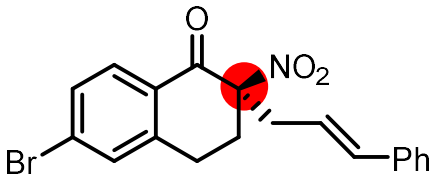


***Tert*-butyl (*R*,*E*)-5-(3-(2-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)-1*H*-indole-1-carboxylate (14):** Tert-butyl 5-allyl-1H-indole-1-carboxylate 5-allylbenzofuran (51.4 mg, 0.20 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (2%→5% EtOAc/hexanes) provided the product as a yellow oil. Run 1 (56.2 mg, 63% yield, 92% ee); Run 2 (56.2 mg, 63% yield, 92% ee); Run 3 (56.3 mg, 63% yield, 92% ee). **Average: 63% (±0.1%) yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 20% isopropanol in hexanes, λ = 254 nm): t_R(major) = 16.544 min, t_R(minor) = 25.050 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.52 (d, *J* = 3.7 Hz, 1H), 6.14 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.24 (ddd, *J* = 14.4, 7.3, 1.3 Hz, 1H), 3.17

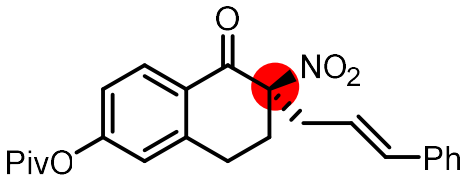
– 3.08 (m, 2H), 3.07 – 2.94 (m, 2H), 2.53 (ddd, J = 14.1, 8.8, 4.5 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.00, 149.59, 142.36, 136.33, 134.88, 134.53, 131.20, 130.84, 130.74, 128.91, 128.84, 127.45, 126.53, 122.69, 120.20, 118.96, 115.19, 107.31, 93.99, 83.82, 38.14, 31.69, 28.20, 25.28; HRMS (ESI): *m/z* calculated for $C_{26}H_{26}N_2O_5$ $[M+H]^+$: 447.1920, found 447.1923. $[\alpha]^{22}_D$ = +2.5° (c = 1.57, $CHCl_3$).



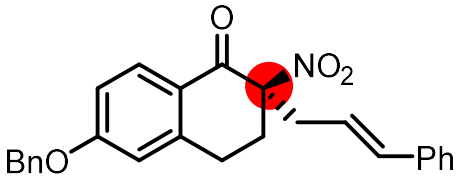
***Tert*-butyl (*R*,*E*)-3-(3-(2-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)-1*H*-indole-1-carboxylate (15):** Tert-butyl 3-allyl-1H-indole-1-carboxylate (51.4 mg, 0.2 mmol, 1 equiv) was reacted according to the general procedure using **L7** with **K_2CO_3 work up**. Purification by flash column chromatography (2%→5% EtOAc/hexanes) provided the product as a clear oil. Run 1 (49.2 mg, 55% yield, 91% ee); Run 2 (48.7 mg, 55% yield, 91% ee); Run 3 (47.7 mg, 53% yield, 91% ee). **Average: 54% (±0.9%) yield, 91% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 65% MeCN in H_2O, λ = 254 nm): t_R(major) = 23.775 min, t_R(minor) = 29.914 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.33 (dd, J = 8.4, 7.2 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.67 (d, J = 15.9 Hz, 1H), 6.23 (dt, J = 15.9, 7.4 Hz, 1H), 3.27 (ddd, J = 14.3, 7.2, 1.3 Hz, 1H), 3.17 – 3.08 (m, 2H), 3.08 – 2.96 (m, 2H), 2.57 – 2.48 (m, 1H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.00, 149.48, 142.32, 135.87, 134.57, 130.75, 128.93, 128.84, 128.42, 127.47, 127.28, 124.77, 124.07, 123.02, 121.85, 119.82, 117.99, 115.39, 93.98, 83.99, 38.72, 31.78, 28.20, 25.28; HRMS (ESI) *m/z* calculated for $C_{26}H_{26}N_2O_5$ $[M+H]^+$: 447.1920, found 447.1916. $[\alpha]^{22}_D$ = +13.2° (c = 1.59, $CHCl_3$).



(*R*)-6-bromo-2-cinnamyl-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (16): 6-bromo-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (108 mg, 0.4 mmol, 2 equiv) was reacted with allylbenzene (26.0 μL, 0.20 mmol, 1 equiv) according to the general procedure in **benzene (0.8 mL)/dioxane (0.8 mL)*** using **L7** with **$NaHSO_3$ work up**. Purification by flash column chromatography (0%→20%→30% DCM/hexanes) provided the product as a clear oil. Run 1 (49.2 mg, 64% yield, 90% ee); Run 2 (47.8 mg, 62% yield, 90% ee); Run 3 (51.3 mg, 66% yield, 90% ee). **Average: 64% (±2.3%) yield, 90% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 70% MeCN in H_2O, λ = 280 nm): t_R(major) = 18.295 min, t_R(minor) = 21.638 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.36 – 7.28 (m, 4H), 7.24 (t, *J* = 7.1 Hz, 1H), 6.57 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.4, 7.4 Hz, 1H), 3.20 (ddd, *J* = 14.3, 7.3, 1.4 Hz, 1H), 3.11 (ddd, *J* = 14.3, 7.6, 1.3 Hz, 1H), 3.06 (m, 1H), 3.02 – 2.89 (m, 2H), 2.47 (ddd, *J* = 14.3, 9.4, 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.08, 143.87, 136.31, 136.23, 131.86, 131.05, 130.37, 130.08, 129.61, 128.62, 128.01, 126.41, 121.30, 93.50, 38.14, 31.61, 24.99. HRMS (ESI) *m/z* calculated for $C_{19}H_{16}BrNO_3$ $[M+H]^+$: 386.0392, found 386.0381. $[\alpha]^{22}_D$ = +43.6° (c = 0.52, $CHCl_3$); **NOTE: while running at standard molarity (0.17 M) gave inconsistent enantioselectivities (88%-90%), running at slightly diluted molarity (0.12 M) resolved the issue, possibly due to improved homogeneity.*

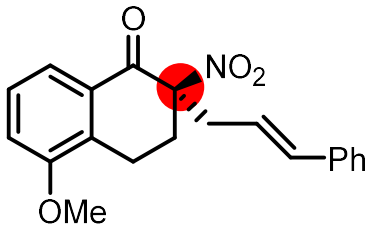


(*R*)-6-cinnamyl-6-nitro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (17): 6-nitro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (116.5 mg, 0.4 mmol, 2 equiv) was reacted with allylbenzene (26.0 µL, 0.20 mmol, 1 equiv) according to the general procedure using **L7** with **$NaHSO_3$ work up**. Purification by flash column chromatography (2%→5%→10% EtOAc/hexanes) provided the product as a clear oil. Run 1 (47.2 mg, 58% yield, 93% ee); Run 2 (45.2 mg, 55% yield, 93% ee); Run 3 (49.7 mg, 61% yield, 92% ee). **Average: 58% (±2.8%) yield, 93% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 60% MeCN in H_2O, λ = 260 nm): t_R(major) = 33.431 min, t_R(minor) = 44.185 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.5, 7.4 Hz, 1H), 3.23 (dd, *J* = 14.5, 7.0 Hz, 1H), 3.14 – 3.06 (m, 2H), 3.03 - 2.92 (m, 2H), 2.50 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.86, 176.37, 155.89, 144.21, 136.36, 136.11, 130.81, 128.61, 128.20, 127.95, 126.42, 121.56, 121.48, 121.14, 93.72, 39.29, 38.04, 31.64, 27.05, 25.33. HRMS (ESI) *m/z* calculated for $C_{24}H_{25}NO_5$ $[M+H]^+$: 408.1811, found 408.1805. $[\alpha]^{23}_D$ = +16.1° (c = 0.64, $CHCl_3$).



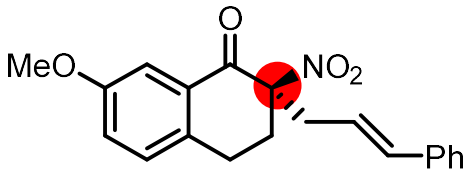
(*R*)-6-(benzyloxy)-2-cinnamyl-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (18): 6-(benzyloxy)-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (60 mg, 0.2 mmol, 2 equiv) was reacted with allylbenzene (13.0 µL, 0.10 mmol, 1 equiv) according to the general procedure using **L7 without work up** (directly dry-loaded onto column). Purification by flash

column chromatography (5%→10% EtOAc/hexanes) provided the product as a clear oil. Run 1 (19.5 mg, 47% yield, 88% ee); Run 2 (20.2 mg, 49% yield, 88% ee); Run 3 (20.0 mg, 48% yield, 88% ee). **Average: 48% (±0.9%) yield, 88% ee**. **Reaction at 25°C: Run 4 (32.4 mg, 78% yield, 84% ee)**. The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 70% MeCN in H_2O, λ = 254 nm): t_R(major) = 28.220 min, t_R(minor) = 33.725 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.28 (m, 9H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.15 (dt, *J* = 15.3, 7.4 Hz, 1H), 5.13 (s, 2H), 3.22 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.10 (dd, *J* = 14.5, 7.4 Hz, 1H), 3.05 (dt, *J* = 11.0, 5.0 Hz, 1H), 3.00 – 2.90 (m, 2H), 2.51 – 2.43 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.48, 163.69, 144.98, 136.46, 135.87, 135.81, 131.47, 128.76, 128.59, 128.38, 127.88, 127.45, 126.39, 124.26, 121.89, 114.90, 113.61, 93.78, 70.28, 38.17, 31.72, 25.60. HRMS (ESI) *m/z* calculated for $C_{26}H_{23}NO_4$ $[M+H]^+$: 414.1705, found 414.1720. $[\alpha]^{22}_D$ = +65.7° (c = 1, $CHCl_3$).



(*R*)-2-cinnamyl-5-methoxy-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (19): 5-methoxy-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (88.5 mg, 0.4 mmol, 2 equiv) was reacted with allylbenzene (26.0 μL, 0.20 mmol, 1 equiv) according to the general procedure using **L7** with **$NaHSO_3$ work up**. Purification by flash column chromatography (2%→5%→10% EtOAc/hexanes) provided the product as a clear oil. Run 1 (43.7 mg, 65% yield, 89% ee); Run 2 (44.8 mg, 66% yield, 90% ee); Run 3 (46.9 mg, 70% yield, 90% ee). **Average: 67% (±2.4%) yield, 90% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK AD-RH column, 0.5 mL/min, 55% MeCN in H_2O, λ = 254 nm): t_R(major) = 37.080 min, t_R(minor)

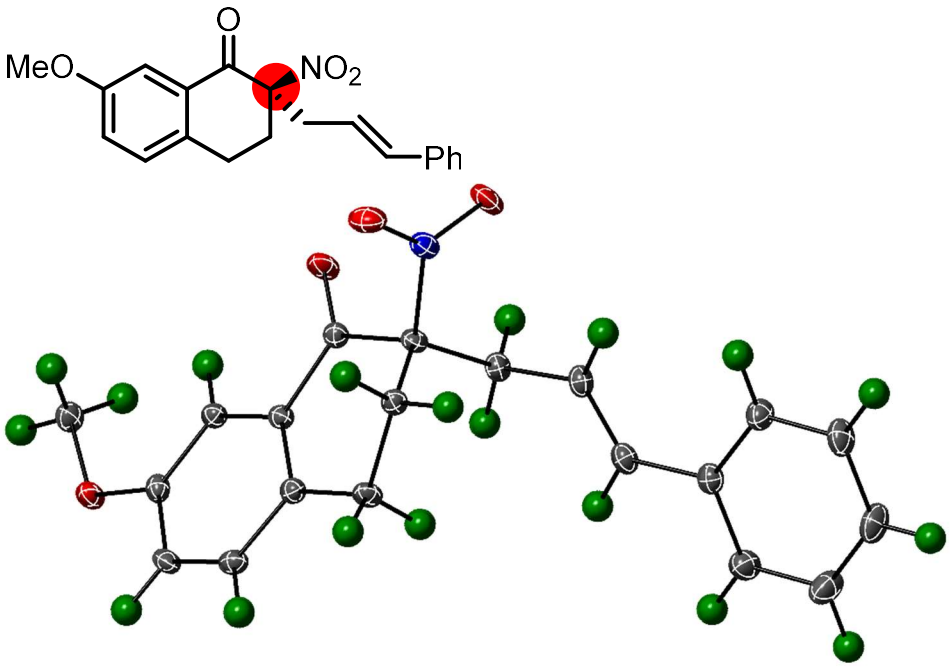
= 57.154 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.17 (dt, *J* = 15.4, 7.4 Hz, 1H), 3.87 (s, 3H), 3.22 (ddd, *J* = 14.6, 7.3, 1.4 Hz, 1H), 3.05 (ddd, *J* = 14.6, 7.8, 1.3 Hz, 1H), 3.01 – 2.90 (m, 3H), 2.49 – 2.39 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.32, 156.68, 136.46, 135.92, 131.54, 131.35, 128.59, 127.89, 127.83, 126.41, 121.69, 120.12, 115.14, 93.86, 55.75, 37.77, 30.79, 19.42. HRMS (ESI) *m/z* calculated for $C_{20}H_{19}NO_4$ $[M+Na]^+$: 360.1212, found 360.1216. $[\alpha]^{22}_D$ = +19.3° (c = 1, $CHCl_3$).



(*R*)-2-cinnamyl-7-methoxy-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (20): 7-methoxy-2-nitro-3,4-dihydronaphthalen-1(2*H*)-one (88.5 mg, 0.4 mmol, 2 equiv) was reacted with allylbenzene (26.0 µL, 0.20 mmol, 1 equiv) according to the general procedure using **L7** with **$NaHSO_3$ work up**. Purification by flash column chromatography (2%→8% EtOAc/hexanes) provided the product as a white powder. Run 1 (38.0 mg, 56% yield, 92% ee); Run 2 (38.7 mg, 57% yield, 92% ee); Run 3 (41.1 mg, 61% yield, 92% ee). **Average: 58% (±2.4%) yield, 92% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 30% isopropanol in hexanes, λ = 254 nm): t_R(major) = 12.481 min, t_R(minor) = 19.875 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 2.7 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.86 (s, 3H), 3.21 (ddd, *J* = 14.4, 7.2, 1.4 Hz, 1H), 3.12 (ddd, *J* = 14.3, 7.6, 1.3 Hz, 1H), 3.07 – 2.91 (m, 3H), 2.51 – 2.44 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.94, 158.84, 136.42, 136.00, 134.95, 131.48, 130.15, 128.60, 127.92, 126.40, 123.30, 121.67, 110.28, 93.81, 55.59, 38.11, 32.05, 24.52;

HRMS (ESI) *m/z* calculated for $C_{20}H_{19}NO_4$ $[M+H]^+$: 338.1392, found 338.1381. $[\alpha]^{23}_D$: +2.9° (c = 0.59, $CHCl_3$). ***Single crystals were grown by recrystallization from warm diethyl ether. The absolute stereochemistry is determined by X-ray crystallography.***

Scheme 1.1: Crystal structure of product 20



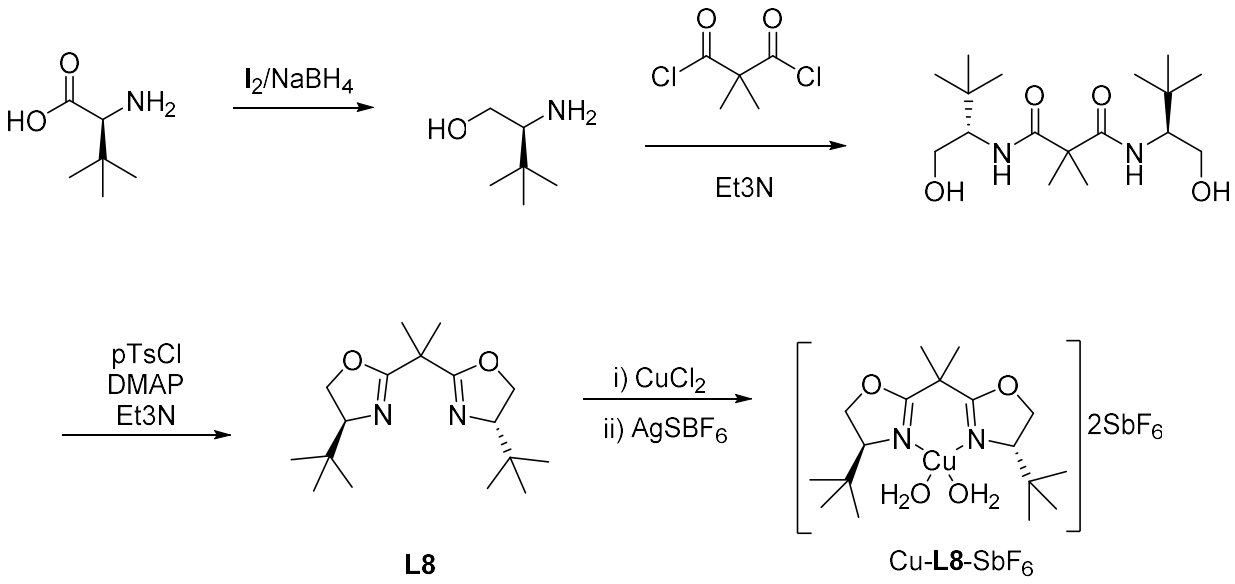
Crystal data and structure refinement for dd48fsa (**3p**).

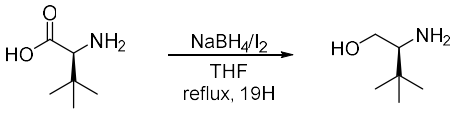
Identification code	dd48fsa	
Empirical formula	C20 H19 N O4	
Formula weight	337.36	
Temperature	110(2) K	
Wavelength	1.54178 ≈	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2794(2) ≈	a= 90∞.
	b = 7.9760(2) ≈	b= 90∞.
	c = 28.9295(8) ≈	g = 90∞.
Volume	1679.66(8) $≈^3$	
Z	4	
Density (calculated)	1.334 Mg/m^3	
Absorption coefficient	0.762 mm^{-1}	
F(000)	712	

Crystal size	0.574 x 0.185 x 0.157 mm^3
Theta range for data collection	3.055 to 68.249∞.
Index ranges	-8<=h<=8, -8<=k<=9, -32<=l<=34
Reflections collected	15671
Independent reflections	3063 [R(int) = 0.0410]
Completeness to theta = 67.679∞	99.9 %
Absorption correction	Integration
Max. and min. transmission	1.0000 and 0.7163
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3063 / 0 / 227
Goodness-of-fit on F^2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0695
R indices (all data)	R1 = 0.0316, wR2 = 0.0709
Absolute structure parameter	-0.01(9)
Extinction coefficient	0.0060(5)
Largest diff. peak and hole	0.221 and -0.171 e.$\approx^{-3}$

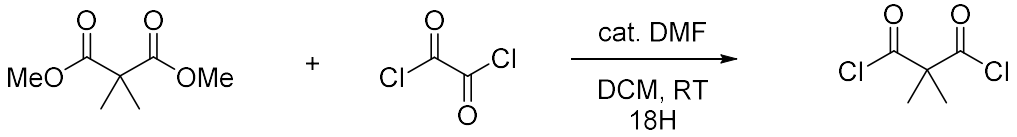
1.4.4: Syntheis of Cu-BOX catalysts for cooperative dual catalysis section

Route Overview:



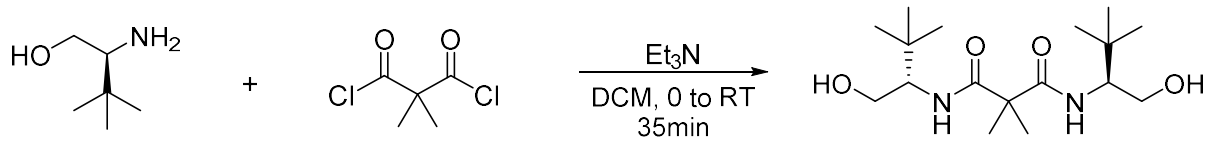


(S)-2-amino-3,3-dimethylbutan-1-ol: An oven dried 3-neck round bottom flask was fitted with an oven dried stir bar and charged with $NaBH_4$ (1.25g, 33mmol, 2.41 eq), L-tbutyl leucine (1.8g, 13.7mmol, 1 eq) and THF (36mL). An addition funnel was added to the middle neck, with two septa on the side necks. In a separate flame dried round bottom flask, I_2 was weighed out and dissolved in THF (9mL). This solution was transferred via syringe to the addition funnel (under N_2 atmosphere). The vessel was cooled to 0 ºC and the I_2 solution was added dropwise to the $NaBH_4$ solution. After the addition was finished, the addition funnel was replaced with a reflux condenser. The solution was heated at reflux for 19 H. Afterwards, the solution was cooled to RT and quenched with MeOH. After concentrating via rotary evaporation, the crude product was mixed with a 5%KOH in water solution and stirred for 16 H at room temperature. The mixture was then transferred to a separatory funnel and extracted 3 times with 150mL of DCM. The combined organic layers were dried over Na_2SO_4, and concentrated. The product was used without any further purification (1.13g isolated, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (ddd, J = 10.2, 4.0, 1.1 Hz, 1H), 3.16 (t, J = 10.2 Hz, 1H), 2.47 (dd, J = 10.2, 3.8 Hz, 1H), 0.86 (s, 9H). Enantiomer: $[\alpha]^{25}_D$ -47.9(c 1.57, $CHCl_3$)

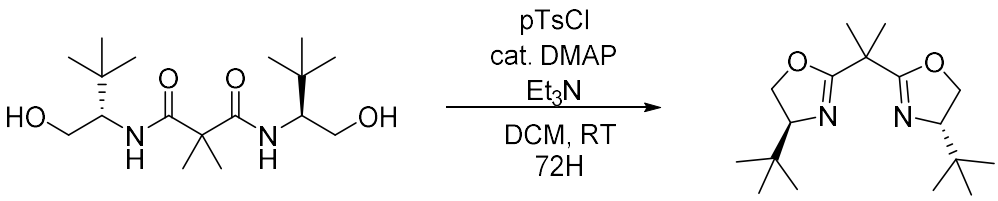


2,2-dimethylmalonyl dichloride: A flame dried round bottom flask fitted with an oven dried stir bar was charged with dimethyl malonic acid (3.17g, 24mmol, 1eq), DCM (24mL), and DMF (242 µL, 3.12mmol, 0.13 eq). The vessel was cooled to 0 ºC, and oxalyl chloride was added dropwise

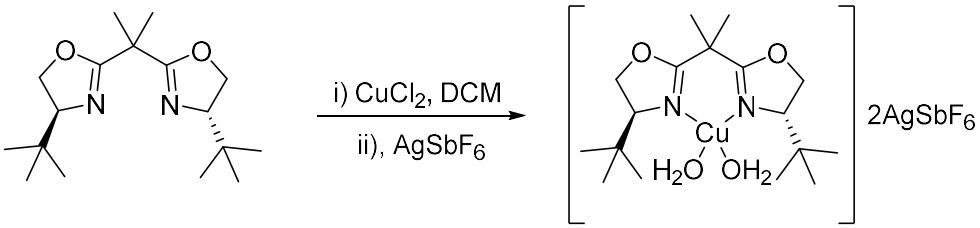
(6.06mL, 72mmol, 3 eq). The ice bath was removed and the solution was heated to RT over 16H. Afterwards, the solution was concentrated via rotary evaporation and diluted with 200mL of DCM. The solution was washed with 5% $NaHCO_3$ 3 times and dried over Na_2SO_4. The product was used without any further purification (3.233g, 81.9% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 9H).



Bis-Amide: A flame dried round bottom flask was fitted with a stir bar and charged with amino alcohol (820mg, 7.0 mmol , 2.25eq) with DCM (11mL). The vessel was placed in an ice bath. Et_3N was added (2.2mL, 15.6mmol, 5eq). In a separate scintillation vial, dimethyl malonyl dichloride (**7**, 526mg, 3.1mmol, 1 eq) was weighed out and dissolved in DCM (4mL). The dichloride solution was added dropwise to the amino alcohol solution. After stirring for 20 min. at 0 °C, the ice bath was removed, and the solution was stirred for 35 min at RT. The crude mixture was diluted with 20mL of DCM. The crude was washed 3 times with H_2O and back extracted each time with DCM. The combined organics were washed one final time with brine and dried over Na_2SO_4. After filtration the product was used without further purification (1.00g 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J = 9.4 Hz, 2H), 3.97 – 3.77 (m, 4H), 3.44 (td, J = 9.6, 1.5 Hz, 2H), 0.93 (s, 18H).



tBu Bis-oxazoline (L8): A flame dried round bottom flask was charged with bis-amide (**10**, 900mg, 2.72, 1 eq), DMAP (33.2mg, 0.272mmol, 0.1eq), and DCM (11mL). The solution was cooled to 0 ºC. Et_3N was added (2.3mL, 16.32mmol, 6eq). In a separate scintillation vial pTsCl (1.04g, 5.44mmol, 2 eq) and suspended in DCM (3mL). The ice bath was removed, and the soliton was stirred for 72 h. Afterwards, the solution was mixed with sat. NH_4Cl. The organic and aqueous layers were separated. The aqueous layer was extracted 3 times with DCM. The combined organics were dried over Na_2SO_4. After filtration and concentration, the residue was purified using flash column chromatography (10% EtOAc/Hex →50% EtOAc/Hex) (269.6mg, 27.0 %yield. Note: the product was only visible under I_2 staining. ^1H NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.01 (m, 4H), 3.84 (dd, *J* = 10.0, 6.9 Hz, 2H), 1.56 (d, *J* = 0.9 Hz, 6H), 0.87 (s, 18H). Enantiomer: $[\alpha]^{25}_D$ +110.9 (c 1.6 $CDCl_3$)



Bis-aquo Cu-BOX SbF_6[Cu-L8-SbF_6]: A fresh, flame dried round bottom flask was fitted with a stir bar and charged with $CuCl_2$ (68.5mg, 0.51mmol, 1 eq), L**8** (150 mg, 0.51mmol, 1eq) and DCM (2mL). Solution stirred under Ar for 3.5 hours. Crude solution transferred to a syringe and filtered through a 0.2µm PTFE syringe filter, concentrated by rotary evaporation, and left under vacuum overnight. DCM (12mL) added to the dry green powder, then $AgSbF_6$ (351mg, 1.02mmol, 2 eq) was added quickly in the dark. The solution was stirred for 2H at RT in the dark. The crude was filtered 3 times through 0.2µm PTFE syringe filter and stored under air. The solution developed a bright blue color indicating the formation of the bis-aquo complex

1.4.4: General Procedure for Cu-BOX additive functionalizations

General Reaction Procedure A (No Cu(II) and **L8** pre-complexation)

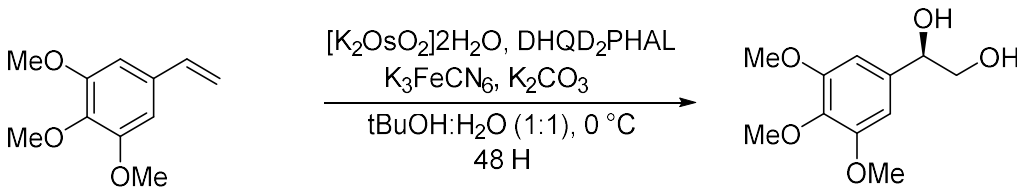
In a typical reaction, a ½ dram vial fitted with an oven dried stir bar was charged with $Pd(OAc)_2$ (2.2mg, 0.01mmol, 0.1 eq), **L3**, (4.2mg, 0.01mmol, 0.1eq) and 0.1mL of Benzene. This mixture was stirred for 30 min at 45 ºC. In a separate ½ dram vial fitted with an oven dried stir bar, the Cu(II) salt (0.01mmol, 0.1 eq unless otherwise indicated) was weighed out with **L6** (3mg, 0.01mmol, 0.1eq unless otherwise indicated) and dissolved in 0.1mL of benzene. This mixture was stirred for 15 minutes at 45 ºC. In another ½ dram vial, 2,6 dimethylbenzoquinone (20.4mg, 0.15 mmol, 1.5 eq), and the nucleophile **1** (14.2mg, 0.1mmol, 1 eq) were weighed out. Allylbenzene (13µL, 0.1mmol, 0.1eq) was added via syringe to the Pd solution. The nucleophile/2,6 DMBQ solution was transferred via pipette to the additive solution. The resulting solution was transferred via pipette to the Pd solution. The mixture was stirred for 20 H at 45 ºC. The mixture was then diluted with ~1mL of DCM. The crude mixture was pushed through a plug silica plug and washed extensively with ethyl acetate. Crude mixture was purified with flash column chromatography (5% EtOAc/Hexane → 10% EtOAc/Hexane). 1HNMR (500 MHz; $CDCl_3$): δ 7.31 (app dt, J = 14.3, 7.3 Hz, 4H), 7.22 (t, J = 7.1 Hz, 1H), 6.45 (d, J = 15.7 Hz, 1H), 6.08 (dt, J = 15.5, 7.7 Hz, 1H), 3.73 (s, 3H), 2.82 (dd, J = 14.0, 7.3 Hz, 1H), 2.56-2.41 (m, 3H), 2.30 -2.23 (m, 1H), 2.08 - 1.98 (m, 2H), 1.97 - 1.88 (m, 1H)

General Reaction Procedure B (Cu(II) and **L6**8pre-complexation)

In a typical reaction, a ½ dram vial fitted with an oven dried stir bar was charged with $Pd(OAc)_2$ (2.2mg, 0.01mmol, 0.1 eq), **L3**, (4.2mg, 0.01mmol, 0.1eq) and 0.1mL of Benzene. This mixture was stirred for 30 min at 45 ºC. In a separate ½ dram vial fitted with an oven dried stir bar, the Cu-

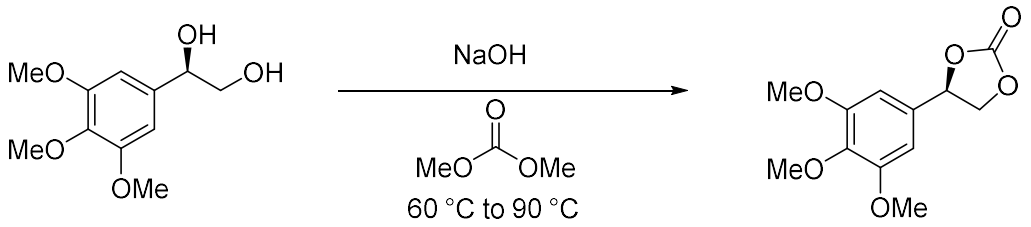
L6-SbF_6 (8.7mg, 0.01mmol, 0.1eq unless otherwise indicated) and dissolved in 0.1mL of benzene. This mixture was stirred for 15 minutes at 45 ºC. In another ½ dram vial, 2,6 dimethylbenzoquinone (20.4mg, 0.15 mmol, 1.5 eq), and the nucleophile **1** (14.2mg, 0.1mmol, 1 eq) were weighed out. Allylbenzene (13µL, 0.1mmol, 0.1eq) was added via syringe to the Pd solution. The nucleophile/2,6 DMBQ solution was transferred via pipette to the additive solution. The resulting solution was transferred via pipette to the Pd solution. The mixture was stirred for 20 H at 45 ºC. The mixture was then diluted with ~1mL of DCM. The crude mixture was pushed through a plug silica plug and washed extensively with ethyl acetate. Crude mixture was purified with flash column chromatography (5% EtOAc/Hexane → 10% EtOAc/Hexane). 1HNMR (500 MHz; $CDCl_3$): δ 7.31 (app dt, J = 14.3, 7.3 Hz, 4H), 7.22 (t, J = 7.1 Hz, 1H), 6.45 (d, J = 15.7 Hz, 1H), 6.08 (dt, J = 15.5, 7.7 Hz, 1H), 3.73 (s, 3H), 2.82 (dd, J = 14.0, 7.3 Hz, 1H), 2.56-2.41 (m, 3H), 2.30 -2.23 (m, 1H), 2.08 - 1.98 (m, 2H), 1.97 - 1.88 (m, 1H)

1.4.4: Typical Synthesis of ArSOX: Synthesis of **L10**

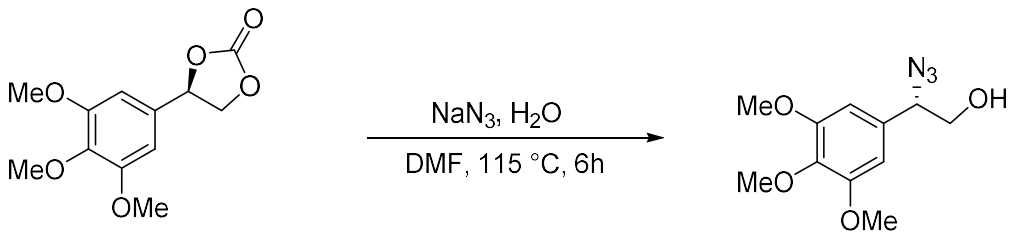


(R)-1-(3,4,5-trimethoxyphenyl)ethane-1,2-diol: A 500mL RBF was fitted with a stir bar and charged with $[K_2OsO_4]2H_2O$ (14.7 mg, 0.04 mmol, 0.002 eq), K_3FeCN_6 (22.1 g, 60 mmol, 3 eq) K_2CO_3 (8.29 g, 60 mmol, 3 eq), $DHQD_2PHAL$ (155.8mg, 0.2 mmol, 0.01 eq),, tBuOH (100 mL), and H_2O (100 mL). While vigorously stirring, the solution was cooled to 0 °C (in an ethylene glycol bath with a chiller probe). After the internal temperature reached 0 °C, the styrene (3.88g, 20 mmol, 1 eq) was added. The solution was stirred for 48 h at 0 °C. Afterwards, the solution was

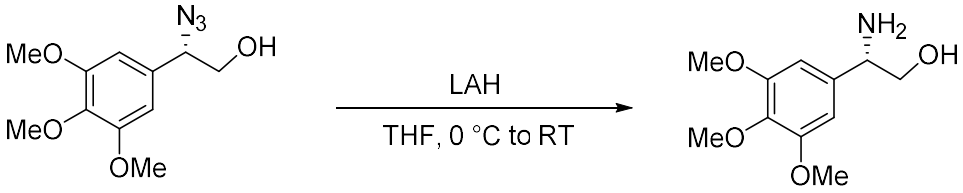
quenched with Na_2SO_3 (30 g), and allowed to gradually warm to room temperature. The solution was diluted with EtOAc and the layers were separated. The aqueous layer was extracted 3 x with EtOAc and dried over Na_2SO_4. Filtration and concentration afforded a pale oil that was used without any further purification in near quantitative yields (4.56 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.59 (s, 2H), 4.76 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.86 (s, 5H), 3.83 (s, 3H), 3.75 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.66 (dd, *J* = 11.2, 8.0 Hz, 1H).



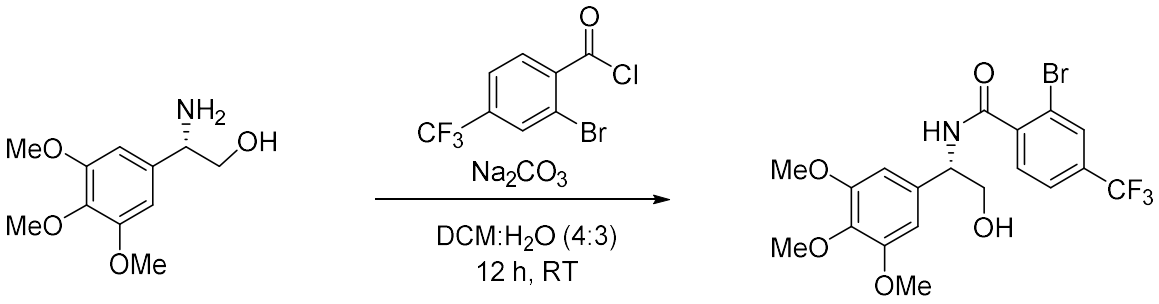
(R)-4-(3,4,5-trimethoxyphenyl)-1,3-dioxolan-2-one: A flame dried RBF was charged with diol (20 mmol, 1 eq), NaOH (1.6g, 40 mmol, 2 eq), and dimethyl carbonate (25 mL). Stir at 60 °C for 2 hours. Heat to 90 °C. A moderate vacuum applied to distill off excess dimethyl carbonate. After ~75% of the dimethyl carbonate was evaporated off, THF/Et_2O added. Filtered through a celite plug. The crude mixture was purified with column chromatography (30% EtOAc/Hexane → 60% EtOAc/Hexane). Combined fractions were repurified via recrystallization (DMC/Hexane) to afford **13** as a white solid (3.21g isolated, 63.1% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.55 (s, 2H), 5.61 (t, *J* = 8.1 Hz, 1H), 4.79 (t, *J* = 8.4 Hz, 1H), 4.33 (dd, *J* = 8.6, 8.0 Hz, 1H), 3.89 (s, 6H), 3.86 (d, *J* = 0.5 Hz, 3H).



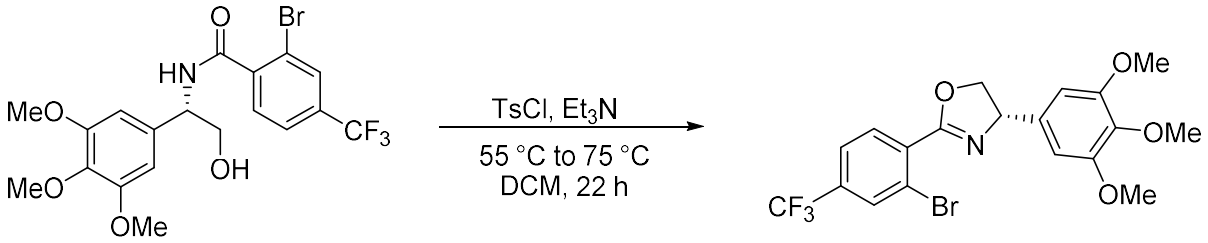
(S)-2-azido-2-(3,4,5-trimethoxyphenyl)ethan-1-ol: A flame dried round bottom flask was charged with H_2O (136 mg, 7.56 mmol, 0.6 eq), NaN_3 (983 mg, 15.12 mmol, 1.2 eq), and carbonate and DMF (27 mL). Solution was heated under N_2 for 7 hours. Afterwards, the crude was diluted with Et_2O, and solids were filtered off with a celite plug. The crude mixture was purified via flash column chromatography (20% EtOAc/Hexane → 35% EtOAc/Hexane) to afford **14** (1.8 g, 56% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.54 (d, *J* = 1.0 Hz, 2H), 4.67 – 4.53 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.74 (t, *J* = 6.2 Hz, 2H).



(S)-2-amino-2-(3,4,5-trimethoxyphenyl)ethan-1-ol: A flame dried round bottom flask was charged with LAH (303.6 mg, 8 mmol, 2 eq), and THF (10 mL). Cool to 0 °C. Azide (1.013g, 4 mmol, 1 eq), was dissolved in THF (10 mL) and added slowly to the LAH solution. The ice bath was removed, and the solution was stirred at room temperature for 3 hours. The solution was cooled to 0 °C. KF (1.6 M, 10 mL) added slowly to quench the LAH. Stir at RT for 20 min. The crude mixture was filtered through a celite plug. The layers were separated. The aqueous layer was extracted 2 x with DCM. Filtration and rotary evaporation afforded **15** as a pale oil (3.40g, 84.9% yield) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.57 (s, 2H), 4.01 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.87 (d, *J* = 1.0 Hz, 6H), 3.84 (d, *J* = 1.0 Hz, 3H), 3.74 (m, 4H (THF overlap)), 3.56 (dd, *J* = 10.6, 8.0 Hz, 1H). $[\alpha]^{22}_D = 19.9^o$ (c = 1.03, $CHCl_3$).

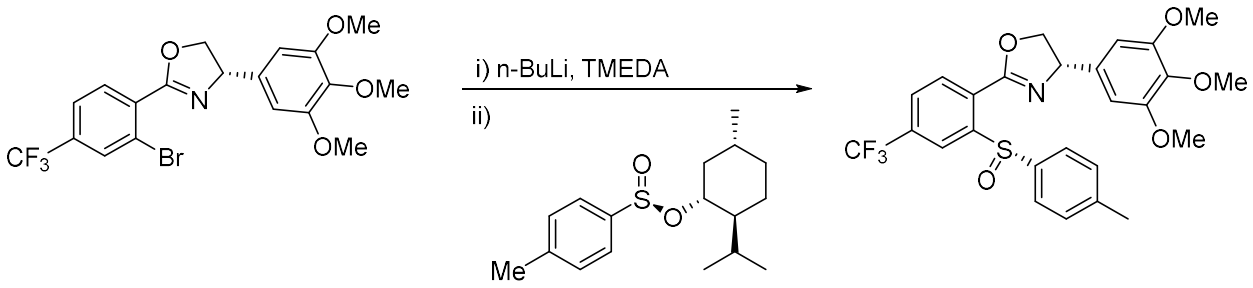


(S)-2-bromo-N-(2-hydroxy-1-(3,4,5-trimethoxyphenyl)ethyl)-4-(trifluoromethyl)benzamide: A flame dried round bottom flask was charged with Na_2CO_3 (830 mg, 7.83 mmol, 3 eq), amino alcohol (593 mg, 2.61 mmol, 1 eq), DCM (8 mL), and H_2O (6 mL). Acyl chloride added dropwise via syringe (862 mg, 3 mmol, 1.15 eq). Stir for 12 hours at room temperature. The organic layer was extracted with DCM (4 x). 1.5 mL of KOH added to organic layer. Stir at RT for 20 min. Quench with 3 M HCl. Layers separated. 2 x extraction with DCM. Dry over Na_2SO_4. Crude mixture was used directly in the next step.



(S)-2-(2-bromo-4-(trifluoromethyl)phenyl)-4-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole: A flame dried round bottom flask was charged with crude amide (approx. 2.61 mmol, 1 eq), TsCl (650 mg, 3.395 mmol, 1.3 eq), Et_3N (1.82 mL, 13.05 mmol, 5 eq) and DCM (20 mL). Stir at 55 °C for 22 hours. Afterwards, 2.5 mL of H_2O added. The vessel was heated to 75 ° for 2 more hours. Cool to RT. The layers were separated. The aqueous layer was extracted 2 x with DCM. Dry over Na_2SO_4. The crude aryl bromide was purified by flash chromatography (20% EtOAc/Hexane → 35% EtOAc/Hexane) to afford **17** (686.4 mg, 57.2 % yield, two steps). ^1H NMR (400 MHz,

Chloroform-*d*) δ 8.00 – 7.94 (m, 1H), 7.90 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.65 (ddd, *J* = 8.1, 1.7, 0.8 Hz, 1H), 6.59 (s, 2H), 5.42 (dd, *J* = 10.3, 8.3 Hz, 1H), 4.85 (dd, *J* = 10.3, 8.5 Hz, 1H), 4.33 (t, *J* = 8.4 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H). $[\alpha]^{22}_D$ = -30.86° (c = 1.05, $CHCl_3$).



(S)-2-(2-((S)-p-tolylsulfinyl)-4-(trifluoromethyl)phenyl)-4-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole: An oven dried round bottom flask was charged with aryl bromide (686.4 mg, 1.49 mmol, 1 eq), and THF (14 mL). TMEDA added (0.22 mL, 1.49 mmol, 1 eq). Cool to –94 °C. n-BuLi (1.6M, 0.93 mL, 1.49 mmol,, 1 eq) was added slowly. Color changed from clear/colourless to blue to green. Stir at –94 °C for 5 minutes. Meanwhile, a flame dried pointy round bottom flask was charged with . (1R,2S,5R)-(−)-Menthyl (S)-p-toluenesulfinate (1.3 g, 4.47 mmol, 3 eq) and dissolved in 9 mL of THF. Lithiated solution transferred to –78 °C bath. Sulfinate solution added slowly (fast drops). Stir at –78 °C for 30 minutes. Stir at 0 °C for 1 hour. Stir at room temperature for 3 h. Quench with saturated NH_4Cl. Layers separated. Extract 2 x with EtOAc. Dry over $MgSO_4$. The crude sulfoxide was purified via flash column chromatography (20% EtOAc/Hexane → 35% EtOAc/Hexane, then 10% Acetone/Hexane → 25% Acetone/Hexane) to afford **L8** as a white powder (156 mg, 30 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.28 (s, 2H), 5.38 (dd, *J* = 10.2, 8.6 Hz, 1H), 4.76 (dd, *J* = 10.2, 8.6 Hz, 1H), 4.27 (t, *J* = 8.6 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 6H), 2.29 (s, 3H). $[\alpha]^{22}_D$ = -68.1° (c = 0.71, $CHCl_3$).

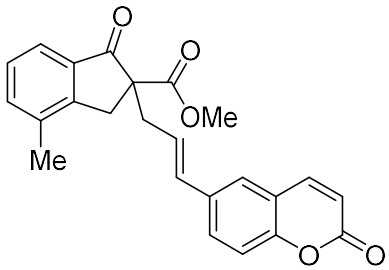
1.4.4: General procedure for initial indanone optimization (Table 1.2.3.1)

General Reaction Procedure C

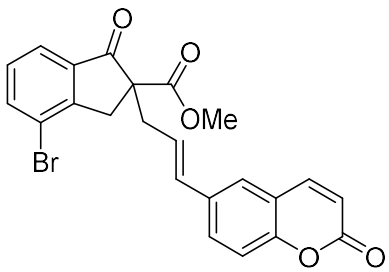
In a typical reaction (Entry 9), a ½ dram vial fitted with an oven dried stir bar was charged with $Pd(OAc)_2$ (2.2mg, 0.01mmol, 0.1 eq), **L7**, (4.2mg, 0.01mmol, 0.1eq) and 0.2 1mL of solvent. This mixture was stirred for 30 min at 45 ºC. In a separate ½ dram vial, **23**(0.2 mmol) was weighed out with $Zn(OAc)_2$ (0.1 mmol), 2,6 dimethylbenzoquinone (20.4mg, 0.15 mmol, 1.5 eq), and **24** (0.1 mmol). This solution was dissolved in 0.3 mL of solvent. This solution and the Pd solution were taken into a 5 °C coldroom. The Pd solution was added quickly to the solution of **23** (solvent may start freezing) with a 0.1 mL solvent wash. The solution was stirred for 72 hours at 5 ° C. The mixture was then diluted with ~1mL of DCM. The crude mixture was pushed through a plug silica plug and washed extensively with ethyl acetate. Crude mixture was purified with flash column chromatography (15% EtOAc/Hexane → 30% EtOAc/Hexane) to afford **25**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.47 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.41 (ddd, *J* = 10.8, 6.4, 1.6 Hz, 2H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 15.7 Hz, 1H), 6.40 (d, *J* = 9.5 Hz, 1H), 6.08 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.72 (s, 3H), 3.68 (d, *J* = 17.4 Hz, 1H), 3.19 (d, *J* = 17.4 Hz, 1H), 3.05 (ddd, *J* = 14.0, 7.3, 1.4 Hz, 1H), 2.77 (ddd, *J* = 14.0, 7.5, 1.3 Hz, 1H). 95 % yield (NMR with nitrobenzene as an internal standard. Enatiomeric excess (%ee) determined by analogy to HPLC traces of reactions with achiral or racemic ligands. 81% ee , CHIRALPAK OJ-H, 20% Isopropanol/Hexanes, 1 ml/min, 66.804 min (minor), 76.51 min (major)

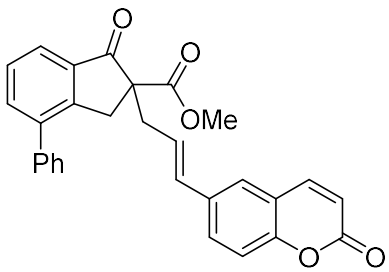
1.4.4: Initial scope for initial indanones (Table 1.2.3.2)



26: 5% EtOAc/Hexane → 10% EtOAc/Hexane. With **L9** instead of **L8**. 81% yield, 83% ee, CHIRALPAK OJ-H, 20% Isoproponal/Hexane, 1 mL/min, RT 45.475 min (minor), 51.715 min (major). Product came out with DMBQ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.9, 2.7 Hz, 2H), 7.48 – 7.39 (m, 2H), 7.36 – 7.28 (m, 2H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.40 (d, *J* = 9.5 Hz, 1H), 6.09 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.72 (s, 2H), 3.60 – 3.51 (m, 1H), 3.13 – 2.98 (m, 2H), 2.75 (ddd, *J* = 14.1, 7.5, 1.3 Hz, 1H), 2.34 (s, 3H).

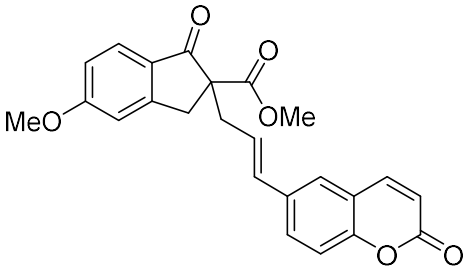


27: 15% EtOAc/Hexane → 30% EtOAc/Hexane. 24% yield, 72% ee, CHIRALPAK OJ-H, 30% Isoproponal/Hexane, 1 mL/min, 29.151 min (major), 43.094 min (minor). Product came out with cinnamyl acetate ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.74 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.65 (d, *J* = 9.6 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.41 (d, *J* = 9.5 Hz, 1H), 6.08 (dt, *J* = 15.6, 7.4 Hz, 1H), 3.73 (s, 3H), 3.61 (d, *J* = 17.8 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.76 (ddd, *J* = 14.1, 7.5, 1.3 Hz, 1H).

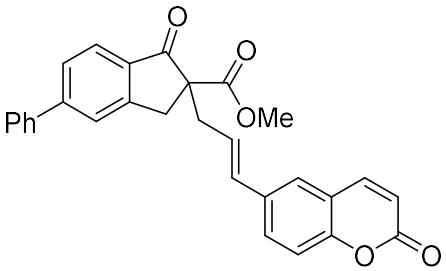


28: 0% EtOAc/Toluene → 2% EtOAc/Toluene. 28% yield, 85% ee, CHIRALPAK OJ-H, 30% Isopropanol/Hexane, 0.25 mL/min 30.055 min (major), 50.875 (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.65 – 7.58 (m,

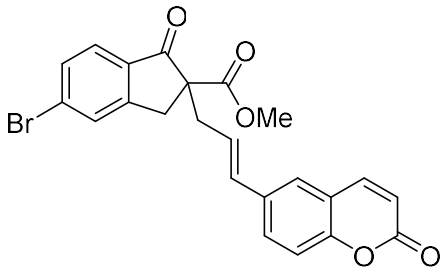
2H), 7.53 – 7.34 (m, 7H), 7.20 (d, *J* = 8.6 Hz, 1H), 6.51 – 6.35 (m, 2H), 6.03 (dt, *J* = 15.9, 7.4 Hz, 1H), 3.72 (s, 4H), 3.14 (d, *J* = 17.5 Hz, 1H), 3.01 (ddd, *J* = 14.3, 7.6, 1.3 Hz, 1H), 2.89 – 2.68 (m, 1H).



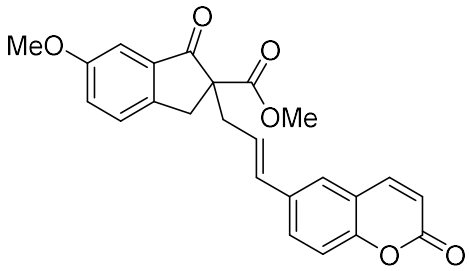
29: With **L9** instead of **L8**. 30% EtOAc/Hexane → 50% EtOAc/Hexane. 96% yield, 81% ee, CHIRALPAK AD-RH, 60% Isopropanol/Water, 26.363 min (major), 31.444 min (minor). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 7.43 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 6.10 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 2H), 3.64 (d, *J* = 17.3 Hz, 1H), 3.14 (d, *J* = 17.3 Hz, 1H), 3.06 (ddd, *J* = 14.1, 7.4, 1.4 Hz, 1H), 2.79 (ddd, *J* = 14.1, 7.4, 1.4 Hz, 1H).



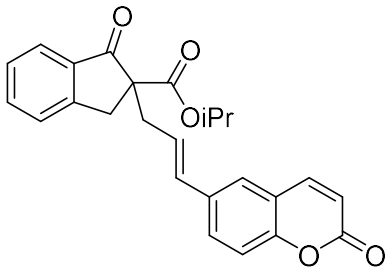
30: 5% EtOAc/Hexane → 10% EtOAc/Hexane. 63% yield, 83% ee, CHIRALPAK AD-RH, 80% Acetonitrile/Water, 0.5 ml/min, 10.193 min (minor), 12.009 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.60 (m, 5H), 7.54 – 7.37 (m, 4H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.40 (d, *J* = 9.5 Hz, 1H), 6.17 – 6.05 (m, 1H), 3.75 (s, 3H), 3.24 (d, *J* = 17.3 Hz, 1H), 3.08 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.81 (dd, *J* = 14.1, 6.9 Hz, 1H).



31: 5% EtOAc/Hexane → 10% EtOAc/Hexane. 10% yield, 74% ee, CHIRALPAK AD-RH, 60% Acetonitrile/Water, 0.5 mL/min, 18.699 min (minor), 21.604 min (major). Product came out as a complex mixture with DMBQ and allylic acetate

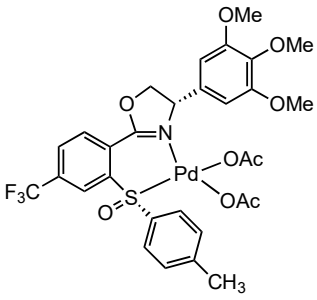


32: 5% EtOAc/Hexane → 10% EtOAc/Hexane. 80% yield, 78% ee CHIRALPAK AD-RH, 50% Acetonitrile/Water, 0.5 ml/min, 21.775 min (minor), 24.43 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 9.6 Hz, 1H), 7.44 – 7.27 (m, 3H), 7.24 – 7.16 (m, 3H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 6.06 (dt, *J* = 15.3, 7.4 Hz, 1H), 3.82 (d, *J* = 0.7 Hz, 3H), 3.70 (d, *J* = 0.7 Hz, 3H), 3.56 (d, *J* = 17.1 Hz, 1H), 3.10 (d, *J* = 17.0 Hz, 1H), 3.06 – 2.96 (m, 1H), 2.81 – 2.65 (m, 1H).

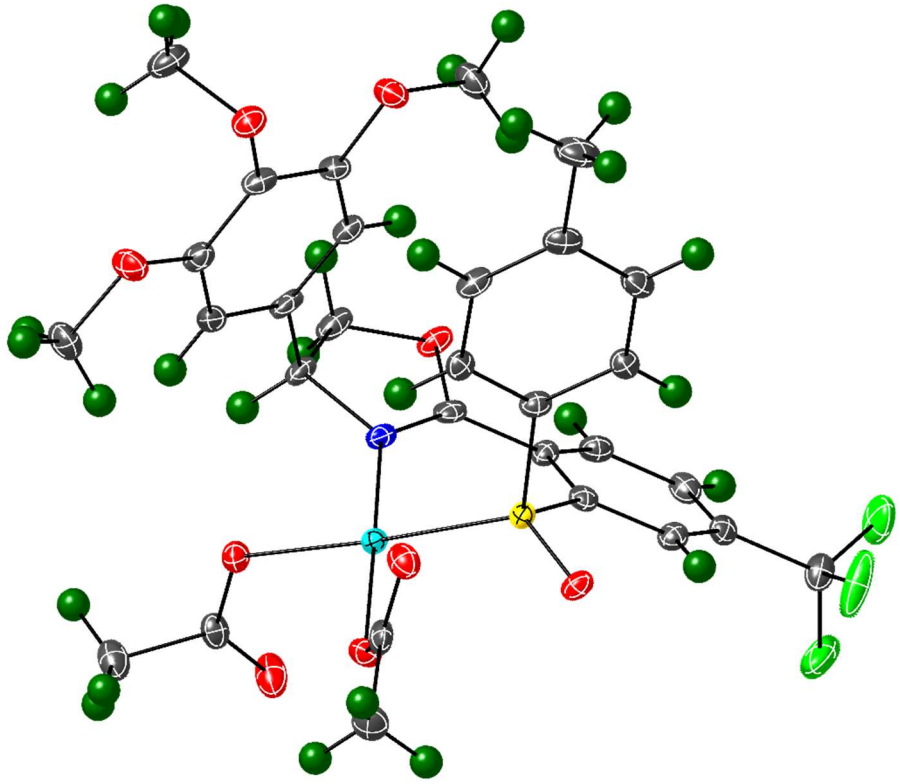


34: With **L9** instead of **L8**. Crude mixture immediately subjected to transesterification reaction to make methyl ester **6ba** 71% yield, 72% ee, CHIRALPAK OJ-H, 20% Isopropanol/Hexanes, 1 mL/min, 64.047 min (minor), 74.698 (major)

1.4.4: Crystal structure for $Pd(OAc)_2$/L10



co-crystallized with 1 equiv. dichloromethane



Crystal data and structure refinement for dd01ls .

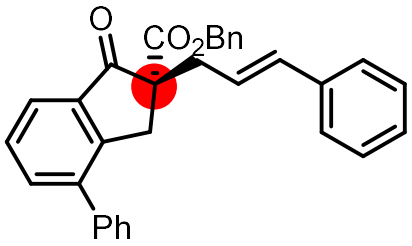
Identification code	dd01ls	
Empirical formula	C31 H32 Cl2 F3 N O9 Pd S	
Formula weight	828.93	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.5175(6) ≈	a= 90∞.
	b = 12.9029(7) ≈	b= 112.9346(17)∞.
	c = 12.3215(6) ≈	g = 90∞.

Volume	1686.34(15) ≈^{3}
Z	2
Density (calculated)	1.633 Mg/m^3
Absorption coefficient	0.841 mm^{-1}
F(000)	840
Crystal size	0.175 x 0.165 x 0.072 mm^3
Theta range for data collection	2.591 to 28.302∞.
Index ranges	-15<=h<=15, -17<=k<=17, -16<=l<=14
Reflections collected	21000
Independent reflections	8294 [R(int) = 0.0265]
Completeness to theta = 25.242∞	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7457 and 0.6863
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8294 / 1 / 440
Goodness-of-fit on F^2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0240, wR2 = 0.0498
R indices (all data)	R1 = 0.0262, wR2 = 0.0508
Absolute structure parameter	-0.029(8)
Extinction coefficient	0.0123(6)
Largest diff. peak and hole	0.497 and -0.463 e.≈$^{-3}$

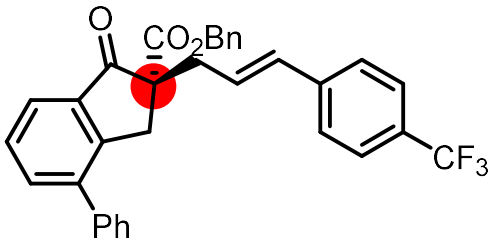
1.4.5: 4-phenyl indanone scope (Table 1.2.5.1)

General procedure D for β-ketoester: To a ½ dram borosilicate vial with stir bar was added ligand **L20** (6.1 mg, 0.01 mmol, 0.1 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv). **Dioxane** (0.3 mL) was added, and the vial was capped and stirred at 45˚C until all solids had dissolved. Separately, to a second ½ dram borosilicate vial with stir bar was added nucleophile, 2,6-dimethylbenzoquinone (20.8 mg, 0.15 mmol, 1.5 equiv) and $Zn(OAc)_2$ dihydrate (11 mg, 0.05 mmol, 0.5 equiv). The catalyst solution was subsequently added to the reaction flask, and dioxane (volume specified below) was used to rinse the catalyst vial, also transferred and added to the

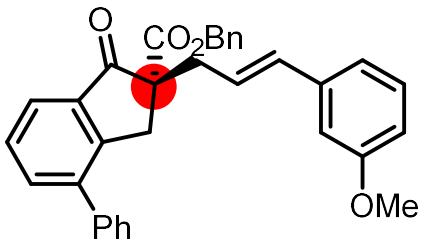
reaction flask. The reaction vial was sealed with a Teflon cap and cooled at 5˚C for 10 min. Allylarene (0.10 mmol, 1 equiv) was then added and the reaction was allowed to stir for 72 hours at 5˚C. Afterward, the reaction mixture was directly subjected to flash column chromatography to provide product.



Benzyl (*R*)-2-cinnamyl-1-oxo-4-phenyl-2,3-dihydro-1*H*-indene-2-carboxylate: Allylbenzene (13.0 μL, 0.10 mmol, 1 equiv) reacted with nucleophile (68 mg, 0.20 mmol, 2 equiv.) in Dioxane (**0.6 mL** total volume) according to the general procedure **D**. Purification by flash column chromatography (5%→8%→10% EtOAc/hexanes) provided the product as a clear oil: Run 1 (36.4 mg, 79% yield, 91% ee); Run 2 (37.7 mg, 82% yield, 91% ee); Run 3 (38.9 mg, 85% yield, 91% ee). **Average: 82% (±2.7%) yield, 91% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 5% isopropanol in hexanes, λ = 254 nm): t_R(major) = 5.261 min, t_R(minor) = 7.151 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.33 – 7.29 (m, 3H), 7.25 – 7.20 (m, 5H), 7.18 – 7.05 (m, 5H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.90 (dt, *J* = 15.8, 7.4 Hz, 1H), 5.10 (s, 2H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.06 (d, *J* = 17.4 Hz, 1H), 2.99 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.69 (dd, *J* = 14.1, 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.92, 170.38, 150.53, 140.33, 138.72, 136.83, 135.71, 135.56, 135.54, 134.22, 128.72, 128.56, 128.47, 128.43, 128.21, 127.91, 127.83, 127.43, 126.21, 124.18, 123.80, 67.27, 60.98, 38.33, 35.88. (missing one carbon in the aromatic region, possibly due to overlapping). HRMS (ESI) m/z calc'd for $C_{32}H_{36}O_3$ [M+H]+: 459.1960; found 459.1945. $[\alpha]^{23}_D$ = +16.0^o (c = 0.68, $CHCl_3$).

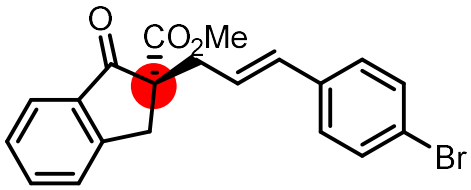


Benzyl (*R*,*E*)-1-oxo-4-phenyl-2-(3-(4-(trifluoromethyl)phenyl)allyl)-2,3-dihydro-1*H*-indene-2-carboxylate (26): 4-trifluoromethylallylbenzene (18.6 mg, 0.10 mmol, 1 equiv) reacted with nucleophile (68 mg, 0.20 mmol, 2 equiv.) in Dioxane (**0.6 mL** total volume) according to the general procedure **D**. Purification by flash column chromatography (5%→8% EtOAc/hexanes) provided the product as a clear oil: Run 1 (40.5 mg, 77% yield, 91% ee); Run 2 (39.6 mg, 75% yield, 91% ee); Run 3 (39.3 mg, 75% yield, 91% ee). **Average: 76% (±1.2%) yield, 91% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 10% isopropanol in hexanes, λ = 254 nm): t_R(major) = 10.815 min, t_R(minor) = 15.988 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.55 – 7.39 (m, 9H), 7.35 – 7.29 (m, 4H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.10 (dt, *J* = 15.4, 7.4 Hz, 1H), 5.24 – 5.16 (m, 2H), 3.79 (d, *J* = 17.4 Hz, 1H), 3.13 (d, *J* = 17.4 Hz, 1H), 3.10 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.80 (ddd, *J* = 14.1, 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.71, 170.27, 150.34, 140.34, 140.22, 138.65, 135.81, 135.49, 135.47, 132.90, 129.18 (q, *J* = 32.4 Hz), 128.76, 128.58, 128.56, 128.45, 128.29, 127.99, 127.90, 127.10, 126.35, 125.38 (q, *J* = 3.8 Hz), 124.15 (q, *J* = 271.9 Hz), 123.86, 67.35, 60.78, 38.30, 36.07. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.46. HRMS (ESI) m/z calc'd for $C_{33}H_{25}O_3F_3$ [M+H]+: 527.1834; found 527.1820. $[\alpha]^{23}_D$ = +10.4° (c = 1.51, $CHCl_3$).



Benzyl (*R*,*E*)-2-(3-(3-methoxyphenyl)allyl)-1-oxo-4-phenyl-2,3-dihydro-1*H*-indene-2-carboxylate (27): 3-allylanisole (14.8 mg, 0.10 mmol, 1 equiv) reacted with nucleophile (68

mg, 0.20 mmol, 2 equiv.) in Dioxane (**0.6 mL** total volume) according to the general procedure **D**. Purification by flash column chromatography (5%→8%→10% EtOAc/hexanes) provided the product as a clear oil: Run 1 (36.8 mg, 75% yield, 92% ee); Run 2 (33.4 mg, 68% yield, 93% ee); Run 3 (33.5 mg, 69% yield, 93% ee). **Average: 71% (±3.9%) yield, 93% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H column, 1 mL/min, 30% isopropanol in hexanes, λ = 254 nm): t_R(major) = 18.424 min, t_R(minor) = 23.131 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.52 – 7.36 (m, 7H), 7.34 – 7.27 (m, 4H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.77 – 6.72 (m, 2H), 6.69 (s, 1H), 6.39 (d, *J* = 15.7 Hz, 1H), 5.97 (dt, *J* = 15.3, 7.4 Hz, 1H), 5.17 (s, 2H), 3.76 (s, 3H), 3.73 (d, *J* = 17.8 Hz, 1H), 3.14 (d, *J* = 17.4 Hz, 1H), 3.06 (dd, *J* = 14.2, 7.7 Hz, 1H), 2.78 (dd, *J* = 13.9, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.95, 170.40, 159.65, 150.55, 140.34, 138.72, 138.30, 135.73, 135.56, 134.16, 129.42, 128.73, 128.56, 128.51, 128.48, 128.44, 128.22, 127.87, 127.84, 124.53, 123.80, 118.88, 113.06, 111.49, 67.27, 60.94, 55.22, 38.27, 35.87. HRMS (ESI) m/z calc'd for $C_{33}H_{28}O_4$ [M+H]+: 489.2066; found 489.2057. $[\alpha]^{23}_D$ = +14.3° (c = 0.7, $CHCl_3$).



Methyl (*E*)-2-(3-(4-bromophenyl)allyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (11a): 4-Bromoallylbenzene (19.7 mg, 0.1 mmol, 1.0 equiv) reacted with nucleophile (38 mg, 0.20 mmol, 2 equiv.) in Dioxane (**0.6 mL** total volume) according to the general procedure **D**. Purification by flash column chromatography (5%→8%→10% EtOAc/hexanes) provided the product as a clear oil: Run 1 (32.6 mg, 85% yield, 79% ee); Run 2 (31.9mg, 83% yield, 79% ee); Run 3 (34.7 mg, 90% yield, 79% ee). **Average: 86% (±3.8%) yield, 79% ee.** The enantiomeric excess was determined by chiral HPLC analysis (CHIRALPAK OJ-H

column, 1 mL/min, 10% isopropanol in hexanes, λ = 260 nm): t_R(minor) = 23.800 min, t_R(major) = 31.201 min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.04 (dt, *J* = 15.6, 7.4 Hz, 1H), 3.72 (s, 3H), 3.67 (d, *J* = 17.3 Hz, 1H), 3.18 (d, *J* = 17.3 Hz, 1H), 3.03 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.73 (dd, *J* = 14.1, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.92, 171.20, 152.92, 135.82, 135.55, 135.01, 133.12, 131.56, 127.89, 127.73, 126.45, 125.27, 124.87, 121.19, 60.25, 52.88, 38.29, 36.14. HRMS (ESI) m/z calc'd for $C_{20}H_{17}BrO_3$ [M+H]+: 385.0439; found 385.0433. $[\alpha]^{23}_D$ = +103.1° (c = 0.385, $CHCl_3$).

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30) Quadrupole moments calculated using Gaussian '09 using the 6-31G** basis set and RHF level of theory. This was similar to the calculations in Ref. 25 and 28. The calculated values were close to the experimental values for benzene (calculated –8.5 buckinghams, observed –8.48 buckinghams) and napthalene (calculated –13.42 buckinghams, observed –13.49 buckinghams)

CHAPTER 2: Allylic C—H Amination of Basic Secondary Amines

Acknowledgements

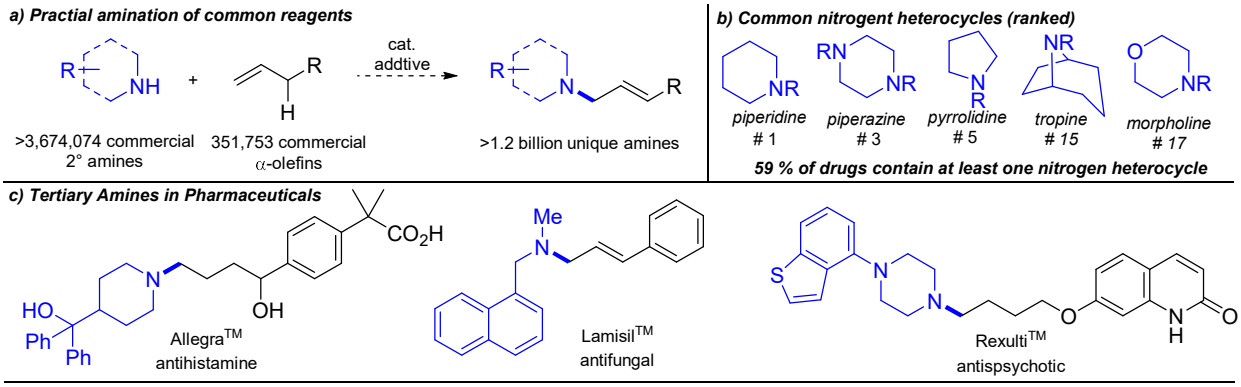
This chapter has been adapted from a current manuscript in preparation.

This work is a collaborative effort. The simple electrophile scope was (**38-50**) was explored by Brenna G. Budaitis, Devon F. A. Fontaine, and Andria L. Pace. The synthesis of naftifine derivatives (**63-65**) and the anti-obesity drug **67** was done by Andria L. Pace and Devon F. A. Fontaine. The synthesis of aripiprazole (**71**) and an aripiprazole analog (**72**) as well as drug derivatives **75**, **76**, and **79** was done by Devon F. A. Fontaine. The clopidogrel derivative **77** was synthesized by Brenna G. Budaitis. These entries are included in this thesis for completeness.

2.1 Introduction

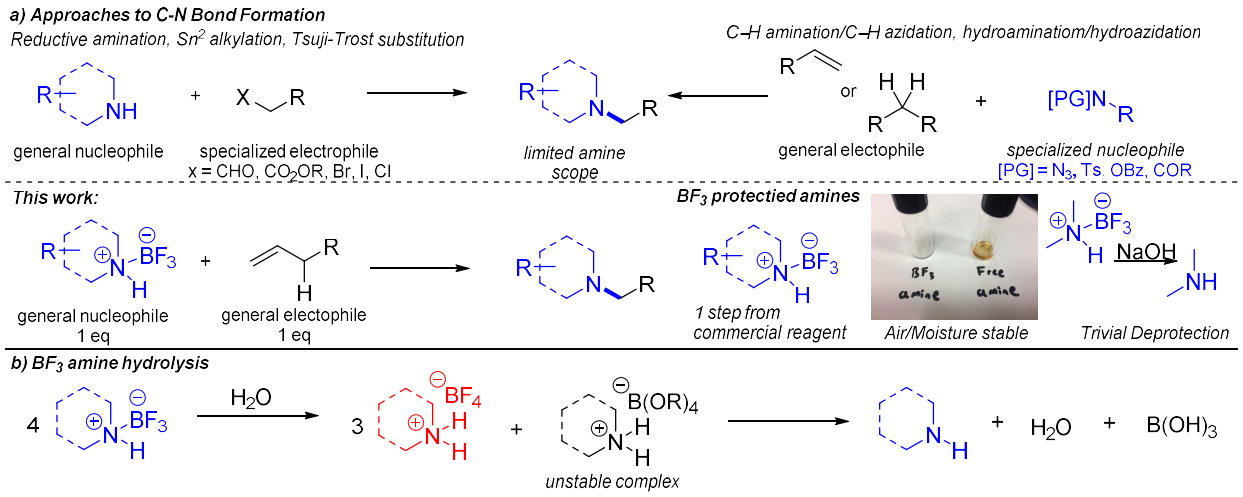
Tertiary amines are one of the most prevalent structures found in modern small-molecule therapeutics. It is estimated that 49% of drug candidates contain aliphatic amines, and of those, 60% are tertiary.[1] In addition, three of the top five nitrogen heterocycles found in pharmaceuticals, piperidines, piperazines, and pyrrolidines, contain a tertiary amine.[2] Due to the importance of this motif, chemists have developed elegant methods to install aliphatic C—N bonds *via* numerous coupling reactions.[3,4] An ideal method would be to directly couple hydrocarbons with secondary amines (Fig 2.1.1). Such a reaction would take advantage of the relative abundance of secondary amines and hydrocarbons to forge a diverse array of tertiary amines.

Figure 2.1: Tertiary Amines



Current coupling methods to synthesize aliphatic tertiary amines fall into two categories (Fig 2.1.2A). The first approach, functionalization of an activated carbon electrophile with a secondary amine, contains traditional C—N bond forming reactions such as N-alkylation *via* nucleophilic substitution[1], reductive amination[5,6], and Tsuji-Trost allylic aminations[7,8]. Such reactions often require the use of unstable, reactive carbon electrophiles including alkyl halogens, aldehydes, and pre-oxidized allylic carbonates respectively, which are often coupled under harshly reductive or basic conditions. These limitations can lead to side reactivity such as overalkylation

Figure 2.2: Approached to C—N bond formation



and elimination in the case of nucleophilic substitution or low functional group tolerance for carbonyls in reductive amination. The second category, intermolecular C—H amination, are methods which functionalize a hydrocarbon with an activated amine source[9–15]. Although these methods successfully convert unactivated C—H bonds to C—N bonds, they are often limited to amine sources that have one or more electron withdrawing groups covalently bound to nitrogen (e.g. Ts, Ac, Tces). This limitation arises from the fact that at high concentrations, unprotected basic aliphatic amines have been demonstrated to bind to electrophilic metal catalysts and inhibit other key steps in the catalytic cycle[16]. Specifically, the Gaunt group has demonstrated that secondary and tertiary aliphatic amines bind strongly enough to Pd metal catalysts to enable directed C—H functionalization[17]. A significant challenge, therefore, in developing a C—H amination reaction to furnish tertiary amines is that under the current paradigm there is no functionality in the secondary amine to which an electron-withdrawing group can be covalently appended. The lack of C—H amination methods which take advantage of the abundance of unprotected secondary amines prompted this investigation their use as potential nitrogen sources. Inspiration was taken by recent advances in metal catalyzed hydroaminations by the Knowles and Buchwald groups, which demonstrated the power of forming tertiary amines from unactivated terminal olefins *via* benzoate-functionalized secondary amines[18,19].

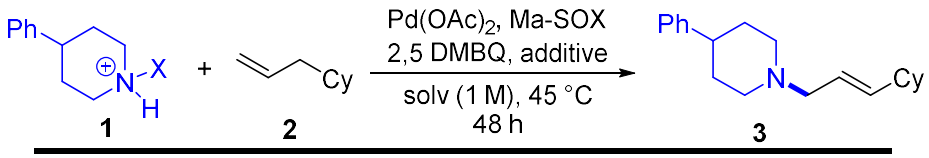
In contrast to aliphatic C—H functionalization, recent advances in allylic C—H functionalization has shown a broad scope in functionalizing allylic C—H bonds with a variety of diverse, relatively unactive nucleophiles. These include oxygen, carbon, and protected nitrogen nucleophiles. Specifically, it has recently emerged that using Pd/sulfoxide-oxazoline catalysis (Pd/SOX), allylic C—H functionalizations may proceed with increased amine scope relative to previous C—H aminations[20,21,22]. The success of this system has been attributed to the ligand's

ability to remain bound to the Pd metal throughout the catalytic cycle, thereby stabilizing a cationic π-allyl Pd intermediate and activating it towards nucleophilic addition of less activated sulfonamide protected primary amines. We questioned whether we could expand the nucleophile scope of this powerful transformation. Specifically, we questioned if secondary amines could be utilized to form tertiary amines. Borontrifluoride (BF_3) is known to form strong dative bonds with secondary amines and prevents secondary and tertiary amines from binding to the respective metal, enabling productive reactivity elsewhere in the molecule[23]. These air, moisture, and column stable BF_3-complexed amine salts can be made in one step from commercially available secondary amines through a simple Lewis acid complexation. Previously reported spectroscopic studies indicate a slow decomposition of amine-BF_3 complexes into free amines and amine-HBF_4 complexes under aqueous conditions[24,25,26]. This slow conversion could potentially be exploited to expose an active nucleophile species from stable amine-BF_3 complexes. This chapter will disclose the C—N coupling of terminal olefins and secondary amines *via* Pd(II)/SOX catalysis and a borontrifluoride complexation strategy, providing a powerful strategy to access valuable tertiary amines. This methodology is remarkably tolerant of numerous classically reactive functionalities, including esters, ketones, aldehydes, and alkyl halides and can be used to access numerous pharmaceutically relevant tertiary amines.

2.2 Results

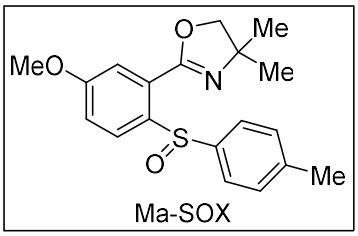
2.2.1 Reaction Development

Table 2.1: General Reaction Development

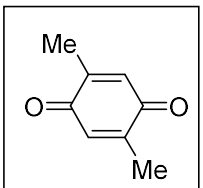


Entry	X	solvent	additive (%)	yield[a]
1	-	Tol.	-	<5%
2	BF_3	Tol.	-	8%
3	BF_3	MTBE	-	25%
4	BF_3	DIOX	-	28%
5	BF_3	DIOX	**A1** (10%)	41%
6	BF_3	DIOX	**A1** (25%)	56%
7	BF_3	DIOX	**A1** (50%)	86%
8	BF_3	DIOX	**A2** (50%)	75%
9	BF_3	DIOX	**A3** (50%)	45%
10	BF_3	DIOX	**A4** (50%)	83%
11	HCl	DIOX	-	<5%
12	HCl	DIOX	**A4** (50%)	<5%
13	TFA	DIOX	-	38%
14	TFA	DIOX	**A4** (50%)	9%
15	TsOH	DIOX	-	46%
16	TsOH	DIOX	**A4** (50%)	<5%
17	HBF_4	DIOX	-	54%
18	HBF_4	DIOX	**A4** (50%)	<5%
19	-	DIOX	**A4** (50%)	<5%
20[b]	BF_3	DIOX	**A4** (50%)	83%
21[c]	BF_3	DIOX	**A4** (50%)	58%
22[d]	BF_3	DIOX	**A4** (50%)	<5%
23	HBF_4	DIOX	**A4** (5%)	75%
24	-	DIOX	**A4** (150%)	64%

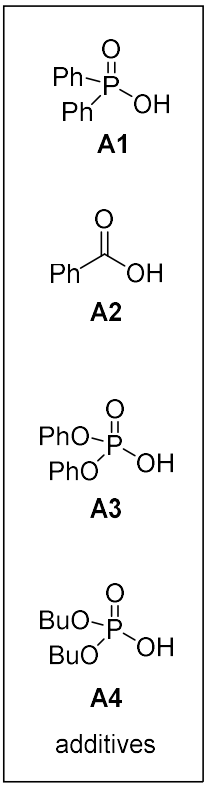
All reactions done with 10% $Pd(OAc)_2$, 10% Ma-SOX, and 1.1 eq of 2,5 DMBQ. In all cases where product was detected, >20:1 *E*:*Z* and >20:1 L:B a) <5% yield determined by crude nmr with CF_3Ph as a standard, all other yields isolated average of two runs b) Crude mixture from BF_3-complexation used instead of purified compound. c) 5% $Pd(OAc)_2$ and 5% Ma-SOX. d) 10% $Pd(OAc)_2$/bissulfoxide as catalyst.



Ma-SOX



2,5 DMBQ



additives

Reaction development began by examining the C—H amination of commercially available 4-phenylpiperidine (**1**) with allylcyclohexane (**2**) using $Pd(OAc)_2$/Ma-SOX catalysis under the previously reported conditions[22]. Expectedly, no product was detected; presumably due to palladium chelation by high concentrations of the free amine (Entry 1). Secondary aliphatic amines readily form stable quaternary complexes with borontrifluoride and at elevated temperatures, amine-borontrifluoride complexes have been shown to convert to HBF_4-amines under Lewis basic conditions (*vide supra*). In addition, boron-trifluoride amines can be purified easily with flash column chromatography and are generally air and moisture stable. A borontrifluoride complex of 1 (**1**-BF_3) gave encouraging reactivity that was significantly enhanced in ethereal solvents like dioxane (Entries 2 to 4). Significantly, no regioisomeric (branched) product or *Z* isomer of the functionalization product (**3**) was observed, highlighting the high regio- and stereoselectivity of this allylic functionalization.

Bronsted acid additives have previously been shown to increase reactivity in Pd(II)-catalyzed allylic C—H functionalizations[27]. The addition of 10 mol% of diphenyl phosphinic acid (**A1**), used recently to increase yield in Pd(II)/SOX catalyzed allylic C—H oxidations, showed an modest increase in yield to 41% (Entry 5)[28]. Increased acid loading followed this trend, with 25 mol % and 50 mol % diphenyl phosphinic acid (**A1**) affording **3** in 56% and 86% respectively (Entries 6 and 7). Diphenyl phosphinic acid is relatively expensive compared to other commercial Bronsted acids. A brief survey of commercially available benzoic acid (**A2**), diphenyl phosphate (**A3**), and dibutyl phosphate (**A4**) revealed that 50 mol % dibutyl phosphate (**A4**) affords similar yields to diphenyl phosphinic acid (**A1**) (Entries 8 to 10). Notably dibutyl phosphate (**A4**) is significantly cheaper than diphenyl phosphinic acid (**A1**). Entry 10 was identified as the optimal conditions for this table.

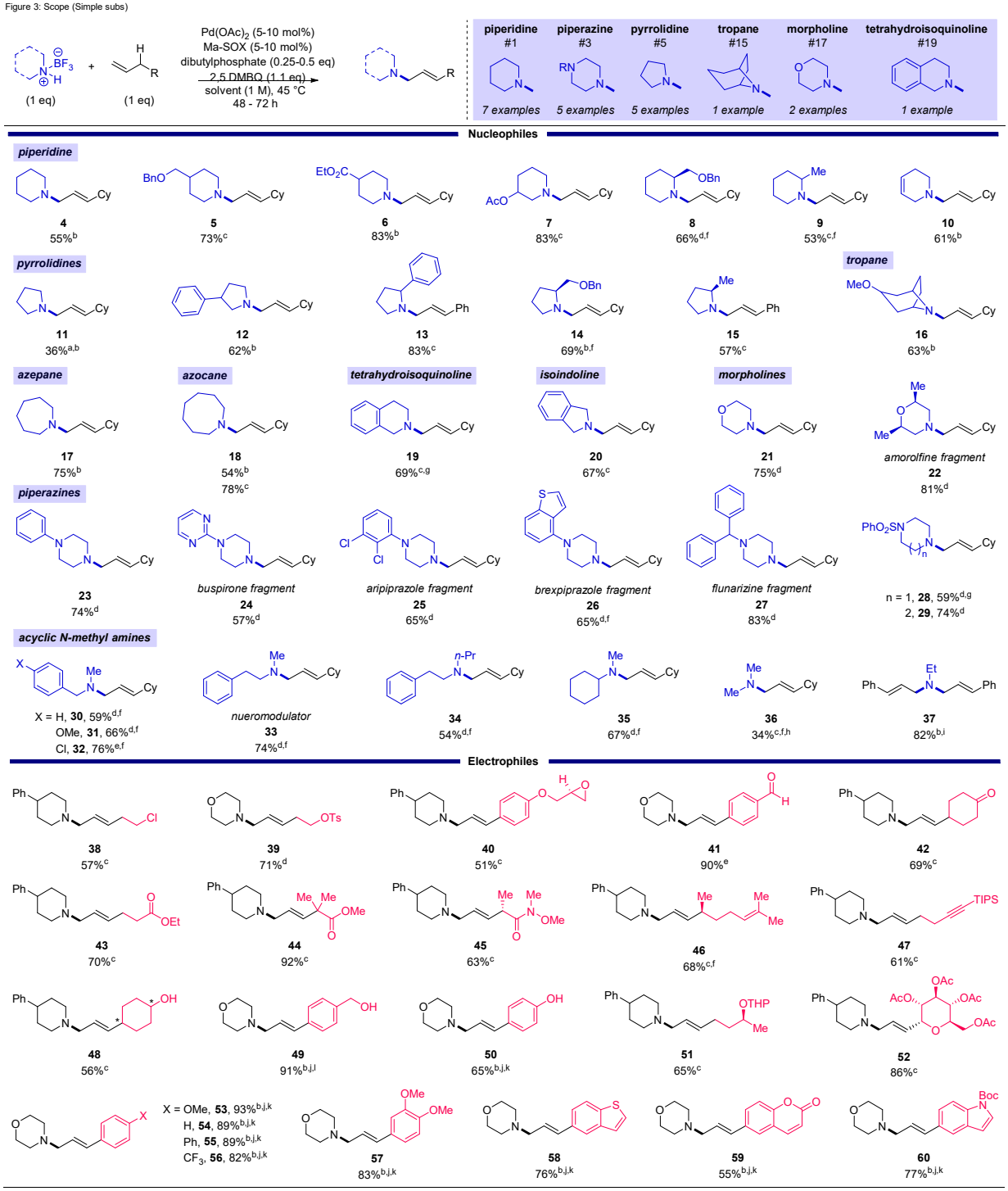
Having established the optimal conditions a series of control studies were performed. One of the products of the hydrolysis of borontrifluoride amine complexes is the HBF_4-amine complex (*vide supra*). A series of Bronsted acid amine complexed were tested as potential alternatives as amine pronucleophiles, including **1**-HCl, **1**-TFA, **1**-TsOH, and **1**-HBF_4 (Entries 11-18). In all cases where product was observed with no dibutyl phosphate additive, increasing the acid additive to the optimal 50 mol% afforded the coupled product in <10% yield, underscoring the unique nature of the amine-borontrifluoride amine in this reaction. In addition, using the free amine (**1**) under these optimal conditions did not restore reactivity (Entry 19). The borontrifluoride amine complexes are typically purified *via* flash column chromatography, however, *in situ* preparation of **1**-BF_3 complex showed no diminishment in yield (Entry 20). The $Pd(OAc)_2$ loading and ligand loading could be decreased to 5 mol % each with a moderate drop in yield (Entry 21, 58%). Finally, the $Pd(OAc)_2$/bis-sulfoxide catalyst used in previous allylic C—H aminations was unable to afford any product, highlighting the unique ability of the Pd(II)/SOX complex to catalyze this transformation (Entry 22)[20,21].

Several experiments were quickly undertaken to indicate the role of the HBF_4-amine complex and role of the dibutyl phosphate additive in this reaction. With minimal acid loading (5 mol%), the **1**-HBF_4 complex can afford the coupled product in 75% yield, around 10% lower than the optimal conditions (Entry 23). In addition, excess dibutyl phosphate (150 mol%) in combination with the free amine (**1**) could moderately restore reactivity to 64% yield (Entry 24). Taken together this information suggests that functionalization can happen with both the free amine and the HBF_4-amine, and more dibutyl phosphate is necessary to promote functionalization in the case of the free amine. For the optimal conditions using the borontrifluoride amine complex, which is hypothesized to hydrolyze to the free amine and HBF_4-amine complex, the optimal 50

mol% acid may be a result of an increase in the concentration of readily available free amine compared to the HBF_4 complex, which only required 5 mol% acid.

2.2.2 Substrate Scope

Table 2.2: Simple Substrate Scope



Unless otherwise indicated all reactions done on a 0.2 mmol scale with 0.1 eq $Pd(OAc)_2$, 0.1 eq Ma-SOX, 1.1 eq 2,5 DMBQ, and 1M molarity. a) 0.167 M. b) 25% dibutylphosphate in dioxane as a solvent. c) 50% dibutylphosphate in dioxane as a solvent. d) 25% dibutylphosphate in toluene as a solvent. e) 50% dibutylphosphate in toluene as a solvent. f) 72 hour reaction time. g) 0.4 mmol scale. h) 0.4 M. i) 0.5 eq of amine-borontrifluoride salt used. j) 0.05 eq $Pd(OAc)_2$ and 0.05 eq Ma-SOX used. k) 24 hour reaction time. l) 12 hour reaction time.

With the optimal conditions in hand, the secondary amine scope was explored, significantly showcasing C—H allylic aminations with 6 different aliphatic amine cores found in pharmaceuticals (Table 2.2.2.1). Saturated amine heterocyles account for 59% of nitrogen moieties in pharmaceuticals, and previous routes *via* C—H aminations often require a multi-step sequence following the amination to access the cyclic amine core[2,29]. Under this C—H allylic amination method, piperidines, pyrrolidines, tropanes, azepanes, and azocanes could all be directly coupled to unactivated terminal olefins to access allylic tertiary amine products **4**-**18** in good yields, using preparatively useful stoichiometries (1 equiv. amine, 1 equiv. olefin). While unsubstituted pyrrolidine and piperidine nucleophiles showed modest amination yields (**4** and **11**), possibly due to competing overalkylation, substitution on the rings with varying functionality significantly afforded increased yields (**5**—**10**, **12**—**15**). Notably, 2-substituted piperidine and pyrrolidine amines containing oxygen functionality did not affect the boron-trifluoride amine complexation. This highlights the remarkable chemoselectivity of boron-trifluoride complexation for amines, allowing for prolinol derivate and its piperidine-homologue to be used as effective nucleophiles to access products **14** and **8** in synthetically useful yields. Consistent with this, additional oxygen functionality can be present at remote sites of the piperidine ring: ethers, acetates, and even esters (known to undergo borontrifluoride etherate catalyzed transesterifications[30]) were all well tolerated (**5**—**8)**. Internal olefins were further well tolerated on both the nucleophile and olefin cross-coupling partner (*vida infra*), underscoring the high chemoselectivity of this allylic functionalization (**10**). Large ring-sized heterocycles including azepane and azocane, as well the topologically more complex alkaloid core tropane, were cross-coupled to allylcyclohexane in preparative yields (**17**, **18**, and **16** respectively). Notably, in cases where functionalization is slow with 25% acid additive (**18**, 54%), increasing the acid loading to 50% proceeded in higher yield

(**18**, 78%). Finally, tetrahydroisoquinoline and isoindoline, cyclic amines with highly oxidizable α-amino C—H bonds that could be problematic with radical based C—H functionalization, were competent nucleophiles under this two-electron process (**19** and **20**).

We next examined cyclic secondary amines nucleophiles housing additional Lewis basic heteroatom functionality, which now may introduce alternative sites for borontrifluoride-complexation, Pd-chelation, or functionalization. Ethereal oxygen, less basic than nitrogen, did not inhibit boron-trifluoride complexation. Morpholine as well as a disubstituted analog, which makes up a core of several antifungals (amorolfine, fenpropimorph, and tridemorph) were readily protected as boron-trifluoride amine salts and successfully underwent allylic C—H amination in preparative yields (**21** and **22**). Piperazines, the 3rd most common amine heterocycle in pharmaceuticals[2], make up a critical component in many pharmaceuticals (e.g. antibiotics, antihistamines, high blood pressure drugs) and are frequently found as *N*-aryl piperazine and cyclizine derivatives. Significantly, selective *N*-aryl piperazine boron-trifluoride complexation and Pd-catalyzed functionalization at the aliphatic secondary amine were unaffected in the presence of the more weakly-basic tertiary arylamine. Several *N*-aryl piperazines, including ones substituted with pyrimidine, halogens, and benzothiophene functionalities were effective nucleophiles for this cross-coupling (**24**—**26**). Cyclizine-based piperazine amines containing a highly basic tertiary aliphatic amine notably underwent boron-trifluoride complexation and C—H allylic functionalization at the secondary amine (**27**). Nucleophiles with strongly inductive withdrawing groups on one of the piperazine nitrogen atoms, such as phenylsulfonyl piperazine and the 7-membered ring homologue, did not deter borontrifluoride complexation or cross-coupling reactivity, and afforded the desired-products **28** and **29** in 59% and 74% yield respectively.

Acyclic secondary amine nucleophiles, which may face additional challenges in boron-trifluoride complexation and allylic C—H functionalization due to higher steric bulk and flexibility, were subsequently investigated. *N*-Methylbenzylamines, common pharmacophores,[32] afforded good yields of cross-coupled products irrespective of the electronic substitution of the benzyl moiety (**30**—**32**). Homologation of the nitrogen alkyl chains, including *N*-methylphenethylamine, a natural amine neuromodulator, and *N*-propylphenethylamine, furnished coupled products with analogous efficiencies (**33** and **34**). More sterically encumbered nucleophiles such as *N*-methylcyclohexylamine could also be used albeit with longer reaction times to afford preparative yields (**35**). Dimethylamine - a small, bulk commodity chemical prevalently found in drugs - afforded the cross-coupled tertiary amine product in modest 34% yield (**36**), with dialkylation to the quaternary amine-salt accounting for the diminished yield. Dialkylation may be taken advantage of, however, to furnish symmetrical tertiary amines from primary amines: starting from commercial starting materials, a streamlined synthesis of the allylic precursor to the smooth muscle relaxant alverine was demonstrated using this method, by reacting one equivalent of ethylamine borontrifluoride salt with two equivalents of allylbenzene (**37**).

Olefin coupling partners were next investigated to demonstrate the generality and orthogonal functional group tolerance of this C—H amination cross-coupling to other methods for constructing tertiary amines. Basic secondary amines are well-precedented in Hoffman alkylation reactions to react with alkyl electrophilic functionality (ca. halogens, sulfonates) to furnish tertiary amines. Under Pd(II)/SOX catalysis with boron-trifluoride complexed amine pronucleophiles, olefins containing remote chloride and tosyl (*p*-toluenesulfonate) react only at the allylic terminus, furnishing allylic amine products (**38** and **39**) with high chemoselectivity. Remarkably, a substrate bearing a disubstituted terminal epoxide, prone to *N*-alkylation with aliphatic amines and able to

polymerization in the presence of borontrifluoride amines, provided the C—H allylic amination product **40** in 51% yield.

Remote electrophilic functionality, generally challenging to maintain in reductive amination methods, was next evaluated. Notably, aldehyde, ketone, ethyl ester, and gem-dimethyl ester functionality is well-tolerated under this method's oxidative conditions and affords excellent yields of tertiary amine products (**41**, **42**, **43**, **44** respectively). Furthermore, Weinreb amide functionality containing an alpha stereocenter afforded 63% of the chiral coupled product (**44**), providing an attractive synthetic handle for further elaboration towards complexity.

Notably, remote functionality prone to oxidation was also well tolerated under this selective oxidative allylic amination. Olefin substrates containing π-functionality such as an internal olefin citronellal-derivative and an internal alkyne afforded the desired products **46** and **47** in synthetically useful yields, with high chemoselectivity for the terminal olefin. Unprotected secondary and primary benzylic alcohols, precedented to undergo oxidation under Pd(II)-catalysis, successfully furnished aminated products **47** and **48** in excellent yields with no detected carbonyl products.[34] Phenol, a well-precedented nucleophile in Pd-catalyzed allylic substitutions, was also well-tolerated to afford allylic amine **45** in 65% yield as the only observed product. It is additionally significant that acid-labile functionality, such as remote tetrahydropyran-protected alcohols and densely functionalized sugars are stable under these mildy acidic amination conditions to furnish products **50** and **51** in preparative yields.

Allylbenzene olefin coupling partners proceeding via activated electrophilic π-allyl intermediates, undergo C—H allylic amination at lower Pd(II)/SOX loadings (5 mol %) and shorter reaction times (12-24 h). Electronic rich, electron neutral, and electron poor aryls in allyl benzene electrophiles uniformly furnished the allylic tertiary amine products in excellent yields

(**52-56**). Common heterocycle motifs found in pharmaceuticals such as benzothiophene, coumarin, and indole are remarkably well-tolerated in furnishing allylic amine products in 76% (**57**), 55% (**58**), and 77% (**59**) yield respectively. Collectively, the mild oxidative nature of this allylic C—H amination cross-coupling provides an orthogonal approach to alkylations, reductive aminations, hydroaminations, and allylic substitutions for furnishing tertiary amines.

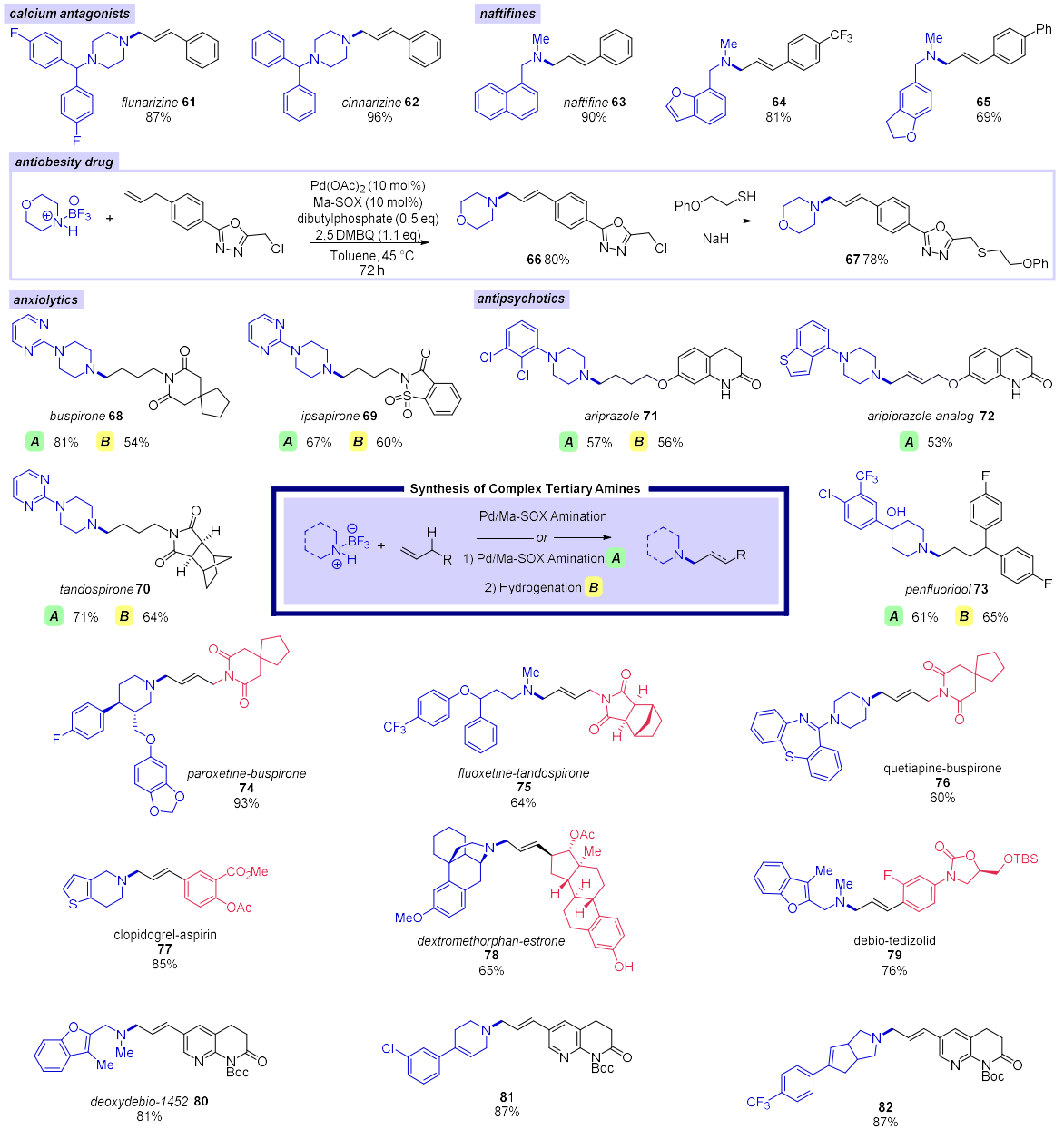
The ability of this allylic C—H amination method to directly cross-couple complex, robust, and commercially and/or readily available fragments towards rapidly furnishing tertiary amine pharmaceuticals and derivatives provides a central advantage to previous methods requiring de-novo syntheses (Figure 2.2.2.1). Starting from commercial piperazines and allylbenzene fragments, calcium antagonists cinnarizine (**62**) and flunarizine (**61**) were furnished in useful yields via Pd(II)/SOX catalysis. Furthermore, naftifine, a classical antifungal, and known analogues (**63**—**65**) were furnished in the cross-coupling of readily accessible *N*-methyl benzylamines with allylated aromatics. A streamlined synthesis of an experimental antiobesity compound **67** was demonstrated in excellent yield, further showcasing the notable chemoselectivity of this allylic amination for terminal olefins over traditional electrophiles: significantly, use of the bifunctional linker housing a terminal olefin and benzyl chloride enabled sequential allylic C—H amination for morpholine installation followed by nucleophilic substitution to install an ethanethiol moiety.[36]

Many psychoactive small molecules are characterized by the linkage of two pharmacophores via a small, saturated aliphatic carbon chains, and are readily accessible via a two-step amination-hydrogenation sequence. Buspirone (**68**), ipsapirone (**69**), and tandospirone (**70**), members of the anxiolytic drug class, were synthesized by cross-coupling pyrimidinylpiperazine to several alkylated imides followed by hydrogenation. The synthesis of

clinical antipsychotics aripiprazole and a similar analog using this approach, however, features functionality traditionally challenging for Pd(II)-catalysis: a *N*-benzothiophene piperazine nucleophile susceptible to sulfur-Pd(II) chelation and/or oxidation, as well as an *O*-alkylated dihydroquinolinone/quinolinone electrophile fragments is prone to competitive beta-alkoxy elimination from a Pd(II) π-allyl intermediate. Remarkably, despite these foreseen challenges, both aripiprazole its analog were furnished in useful yields *via* this C—H amination/hydrogenation sequence (**71** and **72**, no hydrogenation necessary). Penfluoridol (**73**), a clinical diphenylbutylpiperidine antipsychotic, was additionally accessed via this allylic coupling/hydrogenation platform in useful yields (61% and 65% respectively). It is notable that the C—H allylic amination proceeded smoothly with a piperidine nucleophile housing a tertiary benzylic ether susceptible to boron-trifluoride chelation as well as a terminal olefin housing a diphenyl unit susceptible to olefin isomerization and an aryl chloride susceptible to Pd(0) mediated oxidative addition.

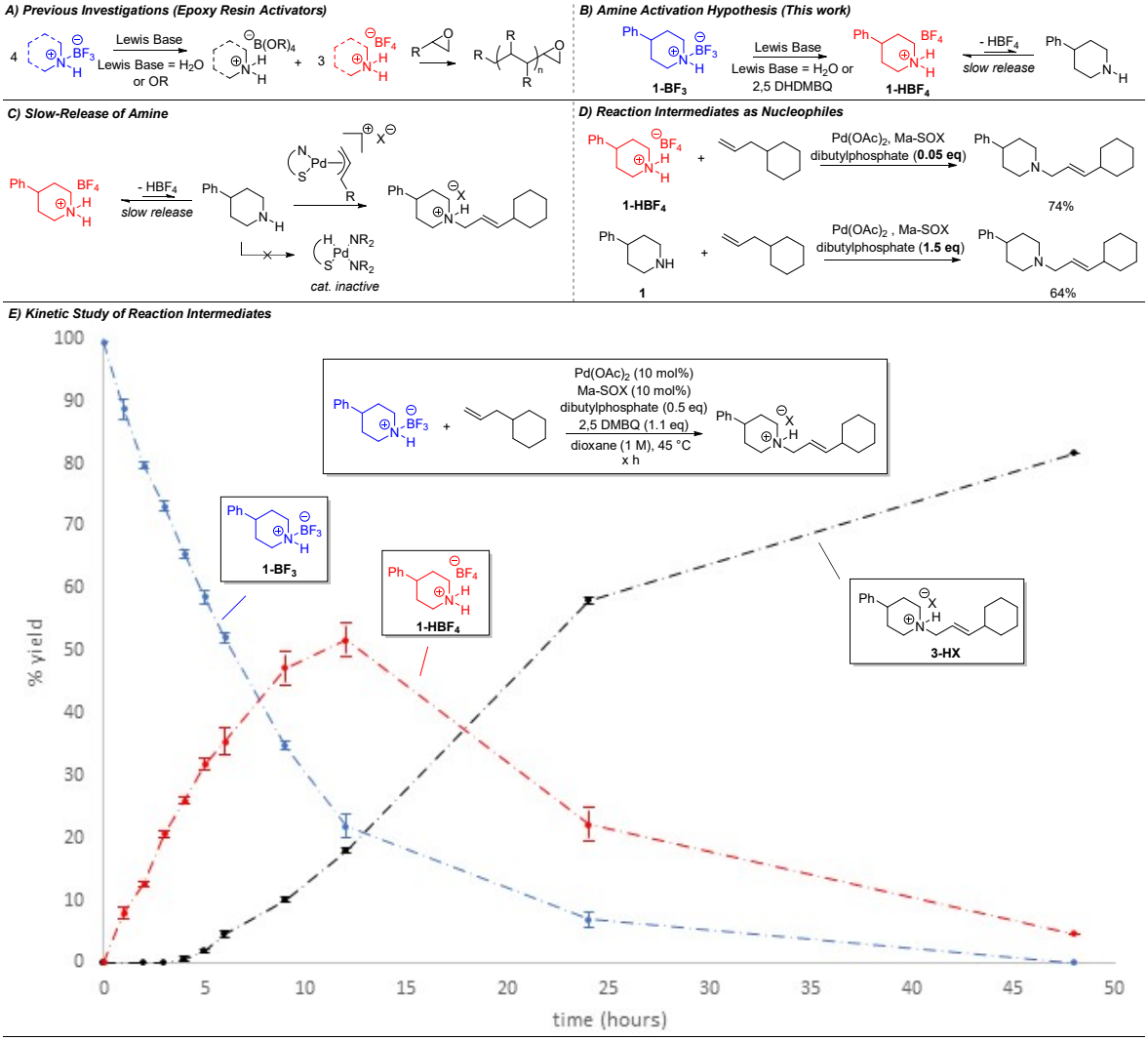
The advantage of this methodology for–late-stage derivatization of clinically relevant compounds and derivatives was demonstrated next. Several commercially available secondary amine drugs or secondary amine drug fragments could be readily derivatized to novel tertiary amine products (**74-79**). Notably, this reaction only requires 1 equivalent of each coupling partner, making it advantageous for coupling synthetically complex terminal olefins with secondary amines. In addition, the mild and selective conditions allow for a diverse collection of functionalities to be well tolerated. The biological importance of the enamide linker in Debio-1452, an antibiotic in phase II clinical trials, can be readily investigated via the cross-coupling of allyl napthapyridone with *N*-Methyl-benzofuranyl amine to furnish deoxydebio-1452 (**80**) as well as tetrahydropyridine and pyrrole deoxygenated derivatives (**81**, **82**).

Figure 2.3: Complex Substrate Scope



2.2.3 Kinetic studies of HBF_4-amine intermediates

Figure 2.4: Kinetic studies of HBF_4-amine intermediates

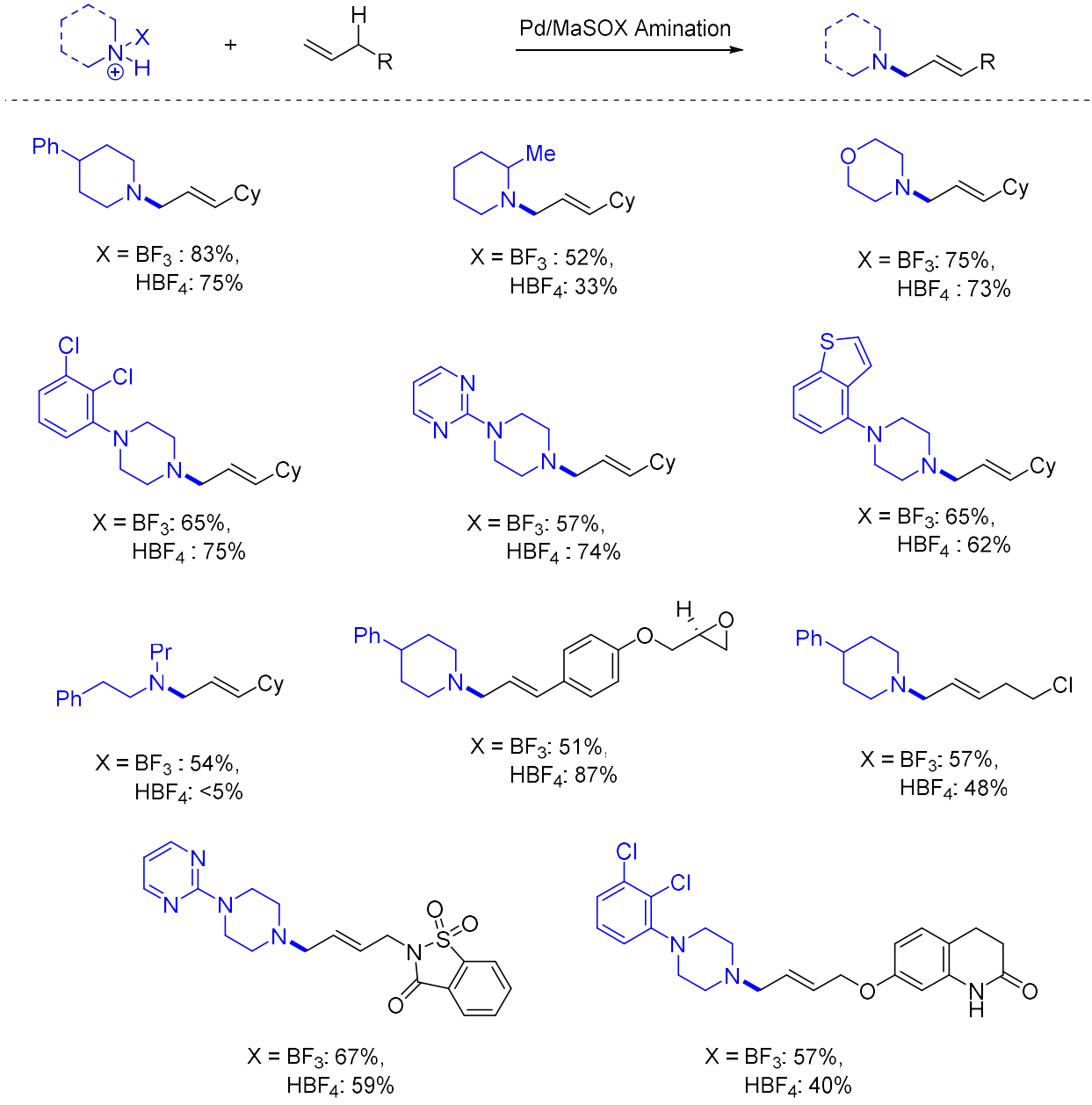


Previous literature on borontrifluoride-amine catalyzed epoxy resin polymerizations indicate that under Lewis basic or aqueous conditions, borontrifluoride-complexed amines are converted to HBF_4-complexed amines (Fig 2.2.3.1A). [24,25,26] These Bronsted acid complexed amines are thought to be responsible for initiating the epoxide polymerization that hardens the resin. Under the allylic C—H amination reaction conditions, trace amounts of water or 2,5 dimethyl benzoquinone could perform a similar role, leading to the release of a Bronsted acid

complexed HBF4-amine (Fig 2.2.3.1B) and another amine borate salt which can quickly decompose to the free amine. This complex now provides a slow release enough free amine to functionalize the electrophilic pi-allyl, while still maintaining useful, unhindered catalytic activity in the presence of Pd(II) (Fig 2.2.3.1C). Re-examining the HBF_4-complexed 4-phenylpiperidine (1-HBF_4), under low acid loadings (5 mol %), reactivity similar to the optimal conditions were observed (*vide supra*), suggesting this could be a competent reaction intermediate (Fig 2.2.3.1D). Furthermore, using a free amine with an excess of acid (1.5 eq) restored useful reactivity, suggesting the quaternization of the amine through an acid prevents metal inhibition. To probe the legitimacy of the HBF_4-amine as a reactive intermediate, the amount of borontrifluoride-amine (**1**-BF_3), HBF_4-amine (**1**-HBF_4), and allylic C—H amination product (**3**-HX) was over time (Fig 2.2.3.1E). Initially, the borontrifluoride-complexed amine is consumed steadily, with quick formation of the HBF_4-complexed nucleophile. Only after an appreciable amount of HBF_4-amine is formed (ca 20-30%) does product formation occur. At the end of the reaction, no borontrifluoride-amine is observed, with only the HBF_4-amine (ca 5%), and product (ca 80%) as the only observed amine species. This data supports the hypothesis that the HBF_4-complexed amine is first formed as an intermediate from the boron-trifluoride-amine, followed by functionalization of the π-allyl.

2.2.4 HBF_4 amines versus borontrifluoride amines

Figure 2.5: Comparison of results of HBF_4 amines and borontrifluoride amines

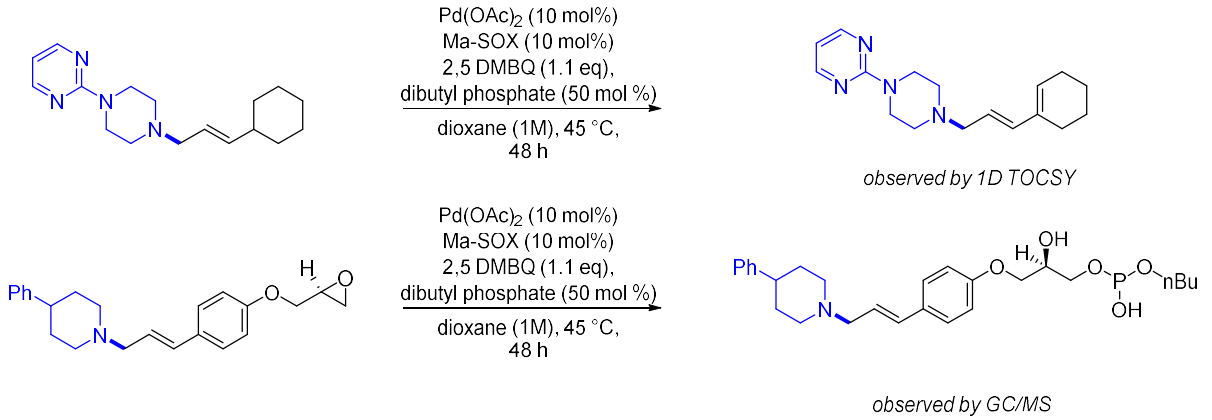


All BF_3 conditions as reproted in table 2.2.2.1. All HBF_4 reactions done with 10 mol% $Pd(OAc)_2$ and 10 mol% Ma-SOX with 0.05 M dibutyl phosphate in dioxane as the solvent.

Having established the similar reactivity between HBF_4 amines and borontrifluoride amines, the potential of using HBF_4 amine salts as a substitute for borontrifluoride amines was investigated. A selection of entries from both the simple and complex substrate tables were

products was synthesized *via* the HBF_4 amine salts and yields were compared to the borontrifluoride amines. For simple piperidine substrates 4-phenylpiperidine and 2-methyl piperidine, the HBF_4 amine performed worse compared to the borontrifluoride amines, potentially due to the relative increase in free amine from the hydrolysis of borontrifluoride amine. For heterocycles with two heteroatoms, either similar or a modest increase in yield (10-20%) yield was observed. A free amine mediated degradation pathway was observed that afforded a diene side product in these cases and limiting the amount of free amine prevented formation of this product (Fig 2.2.4.2). For the acyclic *N*-propyl phenethylamine, no product was observed from the HBF_4-amine product; This unstable amine salt likely decomposes quickly under the reaction conditions.

Figure 2.6: Side products observed

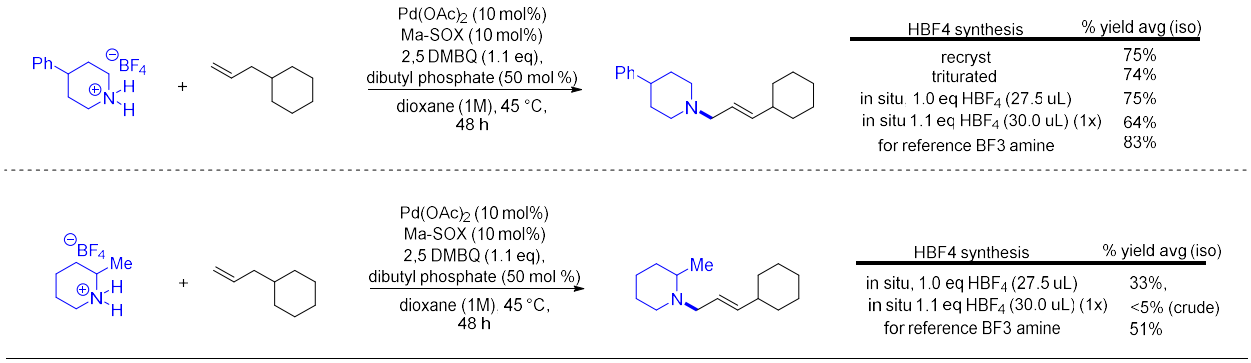


The HBF_4 salt of the 4-phenyl piperidine was investigated with two potentially sensitive olefin coupling partners, an epoxide and alkyl chloride. Although the alkyl chloride aligned with previous piperidine results, the epoxide outperformed the optimal conditions with the borontrifluoride amine. A quick investigation revealed a dibutyl phosphate adduct side product, which likely is formed more in the borontrifluoride reaction, since more dibutyl phosphate is required for optimal reactivity (Fig 2.2.4.2). Finally, the complex substrates that lead to ipsapirone and aripiprazole did

not show an increase in yield switching to the HBF_4 amine salt, similar to the piperidine amines. Collectively, in the majority of cases, the HBF_4-amine performs similarly or slightly poorer compared to the borontrifluoride amines. In cases where the HBF_4 amine is better, the formation of a side product formed in the borontrifluoride reaction is inhibited.

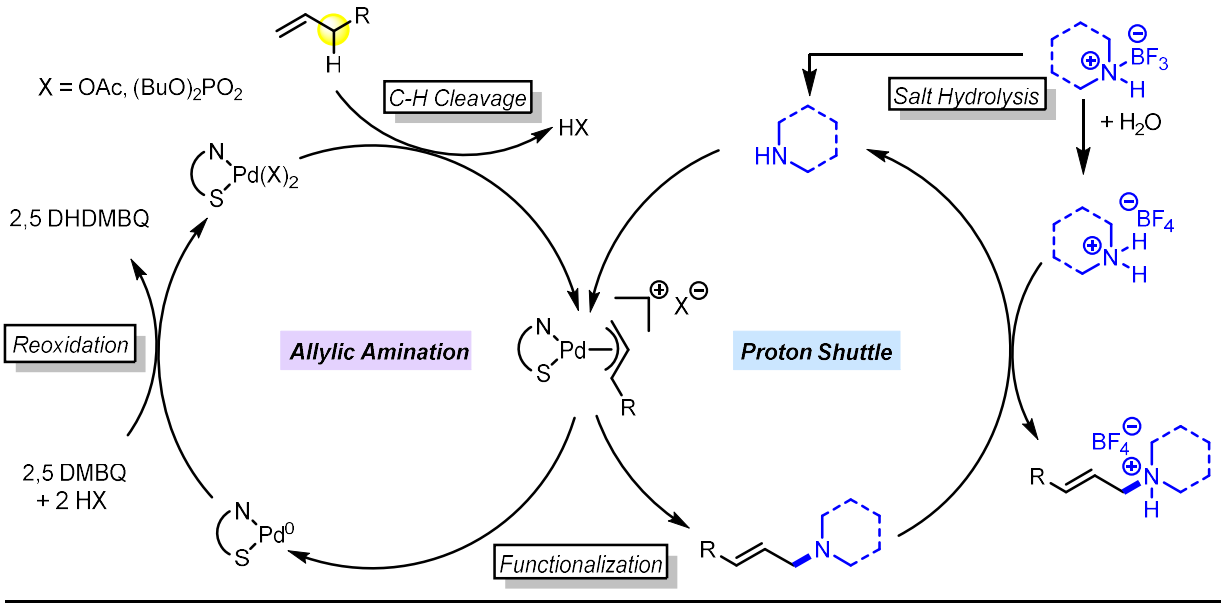
Although on average the HBF_4 amines and borontrifluoride amines were comparable as coupling partners, the borontrifluoride amines are significantly easier to access. All the borontrifluoride amines used in this work could be purified *via* column chromatography. The HBF_4 amines could only be purified by recrystallization or trituration in cases where the amine salts were solid. In several cases where only *in situ* protection of the amine as an HBF_4 salt was viable, even a small excess in added HBF_4•OEt_2 could lead to a significant decrease in yield (Fig 2.2.4.3). In the case of the HBF_4 salt of 4-phenyl piperidine, a solid amine salt, similar yields of the coupled product were observed for a variety of purified amine methods (recrystallization, trituration, or no purification). However, a slight excess of HBF_4•OEt_2 used in the synthesis of the salt (1.1 eq) led to a 10% decrease in the yield of the coupled product. This decrease in yield is likely due to a side reaction of the olefin with the excess HBF_4•OEt_2. This trend was more pronounced in the case of 2-Me-piperidine, which is a liquid as an HBF_4 salt and cannot be purified through recrystallization or trituration and must be made through an *in situ* protection. A slight excess of HBF_4•OEt_2 used to synthesize this salt (1.1 eq) led to no formation of the desired couple product. The borontrifluoride salt; which was also a liquid was purified by simple column chromatography and afforded higher yields of the coupled product.

Figure 2.7: Comparison of HBF_4 amine synthesis methods



2.2.5 Proposed Catalytic Cycle

Figure 2.8: Proposed Catalytic Cycle



The following catalytic fits with the preceding mechanistic data and previous investigations into Pd/SOX catalyzed allylic C—H functionalization.[22] First, the borontrifluoride amine can be hydrolyzed to form the free amine and amine-HBF_4 complex. Next, the Pd(II)/SOX complex can undergo an allylic C—H cleavage event with a terminal olefin to form a π-allyl intermediate. Next, this electrophilic π-allyl can be functionalized with the free amine generated from the initial hydrolysis. This will release a Pd(0)/SOX complex which can be oxidized by the added terminal

oxidant, 2,5 dimethyl benzoquinone. The free tertiary amine formed in the functionalization can undergo a proton transfer with the secondary amine HBF_4 complex to generate some free amine that can be used in the next catalytic cycle.

2.3 Conclusion

In summary we have developed the first allylic C—H amination with quaternized secondary amines to produce tertiary amines. This novel reaction relies on complexation of the amine with a borontrifluoride; a Lewis acid which prevents deleterious inhibition of the Pd-center while allowing a slow release of free amine. The cross-coupling is general for a variety of amine classes, and these amines can be coupled to olefins containing amine-sensitive, oxidatively-labile, and acid-labile functionality. This methodology can be applied to make numerous commercial and experimental therapeutics, as well as several drug derivatives, indicating its utility in the development of medicinally relevant chemical products.

2.4 Experimental

2.4.1 General Information

All commercially obtained reagents were used as received; $Pd(OAc)_2$ (Johnson-Matthey Chemicals, high purity) was stored in a glove box, and weighed out in the air at room temperature prior to use. Toluene and dioxane was purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). 2,5-Dimethylbenzoquinone was purchased from TCI and used as received. All allylic C–H amination reactions were set up and run under ambient air with no precautions taken to exclude moisture. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV,

potassium permanganate, ninhydrin, and iodine stains. Flash chromatography was performed using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.) or basic Brockmann Grade 1 alumina (58 Å, 60 mesh powder, 205 m^2/g). Brockmann Grade 3 alumina was made by mixing Brockmann Grade 1 alumina with 6 wt. % H_2O.

^1H NMR spectra were recorded on a Varian Unity-u400nb (500 MHz), Varian Inova-500 (500 MHz), Varian Unity-500 (500 MHz), or Carver-Bruker 500 (125MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, sext. = sextet, sept. = septet, o = octet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Carver-Bruker 500 (125MHz) or Varian Unity-500 (125MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$). ^{19}F NMR spectra were recorded on a Carver-Bruker 500 (125MHz) or Varian Unity-500 (470 MHz) spectrometer and are reported in ppm using C_6F_6 as an external standard ($CDCl_3$). Optical rotations were measured with a sodium lamp using a 1 mL cell with a 50 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_\lambda T^oC$ (*c* = g/100 mL solvent). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer, and electron ionization (EI) and field desorption (FD) spectra were performed on a Micromass 70-VSE spectrometer.

2.4.2 Reaction Development

General Procedure:

To a ½ dram vial with stir bar was added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq) Ma-SOX (6.9 mg, 0.02 mmol, 0.1 eq), 4-phenylpiperidine-complex (0.2 mmol, 1 eq) and 2,5 dimethylbenzoquinone (30 mg, 0.22 mmol, 1.1 eq). A fresh solution of the additive in solvent was added (0.2 mL, 1M), followed by allyl cyclohexane (31 μL, 0.2 mmol, 1 eq). The vial was sealed with Teflon tape and parafilm to prevent any liquid from escaping, and placed in a 45 °C aluminum block. The mixture was stirred at 45 °C for 48 h. The crude mixture was then diluted with 25 mL of EtOAc and washed with 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO^3$, then 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO_3$, then 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO_3$, then 5 mL of 1 M NaOH (7 washes in total). Purification *via* column chromatography (Brockmann Grade 3 basic alumina, 0%→5%→10% EtOAc/Hx) afforded (*E*)-1-(3-cyclohexylallyl)-4-phenylpiperidine (**3**) as a red oil.

Entry 1: The general procedure was followed using 4-phenylpiperidine (32.3 mg, 0.2 mmol, 1 eq) as the nucleophile and toluene as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

Entry 2: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and toluene as the solvent. Run 1: 3.9 mg, 7% yield. Run 2: 5.0 mg, 9% yield. **Average: 8% yield**.

Entry 3: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and methyl tert-butyl ether as the solvent. Run 1: 14.8 mg, 26% yield. Run 2: 13.3 mg, 23% yield. **Average: 25% yield**.

Entry 4: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and dioxane as the solvent. Run 1: 15.8 mg, 28% yield. Run 2: 15.8 mg, 28% yield. **Average: 28% yield**.

Entry 5: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.1 M diphenyl phosphinic acid in dioxane (0.2 mL, 0.02 mmol, 0.1 eq) as the solvent. Run 1: 22.9 mg, 40% yield, Run 2: 22.5 mg, 40% yield. **Average: 40% yield**.

Entry 6: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.25 M diphenyl phosphinic acid in dioxane (0.2 mL, 0.05 mmol, 0.25 eq) as the solvent. Run 1: 31.8 mg, 56% yield, Run 2: 31.6 mg, 56% yield. **Average: 56% yield**.

Entry 7: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M diphenyl phosphinic acid in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 47.7 mg, 84% yield, Run 2: 50.1 mg, 88% yield. **Average: 86% yield**.

Entry 8: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M benzoic acid in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 43.0 mg, 76% yield, Run 2: 41.5 mg, 73% yield. **Average: 75% yield**.

Entry 9: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M diphenyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 25.7 mg, 45% yield, Run 2: 25.6 mg, 45% yield. **Average: 45% yield**.

Entry 10: The general procedure was followed with 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 47.5 mg, 84% yield, Run 2: 46.8 mg, 83% yield. **Average: 83% yield**.

Entry 11: The general procedure was followed with 4-phenylpiperidin-1-ium chloride (39.5 mg, 0.2 mmol, 1 eq) as the nucleophile and dioxane as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

Entry 12: The general procedure was followed with 4-phenylpiperidin-1-ium chloride (39.5 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

Entry 13: The general procedure was followed with 4-phenylpiperidin-1-ium trifluoroacetate (55.1 mg, 0.2 mmol, 1 eq) as the nucleophile and dioxane as the solvent. Run 1: 20.8 mg, 37% yield, Run 2: 21.8 mg, 38% yield. **Average: 38% yield**.

Entry 14: The general procedure was followed with 4-phenylpiperidin-1-ium trifluoroacetate (55.1 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 5.4 mg, 10% yield, Run 2: 4.4 mg,8% yield. **Average: 9% yield**.

Entry 15: The general procedure was followed with 4-phenylpiperidin-1-ium tosylate (66.7 mg, 0.2 mmol, 1 eq) as the nucleophile and dioxane as the solvent. Run 1: 26.1 mg, 46% yield, Run 2: 25.6 mg, 45% yield. **Average: 46% yield**.

Entry 16: The general procedure was followed with 4-phenylpiperidin-1-ium tosylate (66.7 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

Entry 17: The general procedure was followed with 4-phenylpiperidin-1-ium tetrafluoroborate (49.8 mg, 0.2 mmol, 1 eq) as the nucleophile and dioxane as the solvent. Run 1: 30.5 mg, 54% yield, Run 2: 30.1 mg, 53% yield. **Average: 54% yield**.

Entry 18: The general procedure was followed with 4-phenylpiperidin-1-ium tetrafluoroborate (49.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1

mmol, 0.5 eq) as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

Entry 19: The general procedure was followed using 4-phenylpiperidine (32.3 mg, 0.2 mmol, 1 eq) with 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

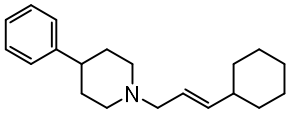
Entry 20: The general procedure was followed with crude (not purified *via* column chromatography) 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.5 M dibutyl phosphate in dioxane (0.2 mL, 0.1 mmol, 0.5 eq) as the solvent. Run 1: 46.2 mg, 81% yield, Run 2: 48.0 mg, 85% yield. **Average: 83% yield**.

Entry 21: The general procedure was followed using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq) with Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq) as the catalyst, 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile, and 0.5M dibutyl phosphate in dioxane (0.1 mmol, 0.5 eq) as the solvent. Run 1: 32.4 mg, 57% yield, Run 2: 33.8 mg, 60% yield. **Average: 58% yield**.

Entry 22: The general procedure was followed using 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (xx mg, 0.02 mmol, 1 eq) as the catalyst, 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) as the nucleophile, and 0.5M dibutyl phosphate in dioxane (0.1 mmol, 0.5 eq) as the solvent. Trace amount of product was observed by crude ^{1}HNMR and no product was isolated.

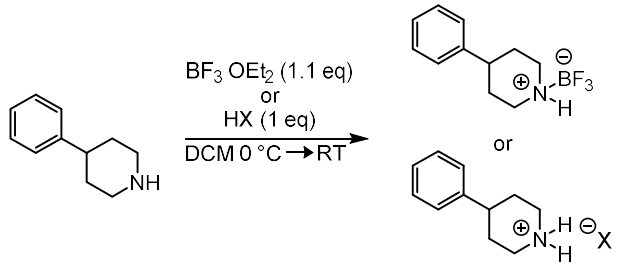
Entry 23: The general procedure was followed with 4-phenylpiperidin-1-ium tetrafluoroborate (49.8 mg, 0.2 mmol, 1 eq) as the nucleophile and 0.05 M dibutyl phosphate in dioxane (0.2 mL, 0.01 mmol, 0.05 eq) as the solvent. Run 1: 42.6 mg, 75% yield, Run 2: 42.6 mg, 75% yield. **Average: 75% yield**.

Entry 24: The general procedure was followed using 4-phenylpiperidine (32.3 mg, 0.2 mmol, 1 eq) with 1.5 M dibutyl phosphate in dioxane (0.2 mL, 0.3 mmol, 1.5 eq) as the solvent. Run 1: 36.1 mg, 64% yield, Run 2: 36.7 mg, 65% yield. **Average: 64% yield**.

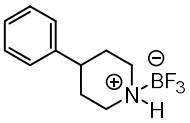


(*E*)-1-(3-cyclohexylallyl)-4-phenylpiperidine (xx): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (app t, *J* = 7.6 Hz, 2H), 7.23 (app d, *J* = 7.0 Hz, 2H), 7.19 (app t, *J* = 7.2 Hz, 1H), 5.56 (dd, *J* = 15.5, 6.1 Hz, 1H), 5.49 (dt, *J* = 15.2, 6.4 Hz, 1H), 3.06 (d, *J* = 11.2 Hz, 2H), 2.97 (d, *J* = 6.4 Hz, 2H), 2.48 (tt, *J* = 10.2, 5.2 Hz, 1H), 2.00 (ddt, *J* = 17.9, 10.7, 5.9 Hz, 3H), 1.91 – 1.78 (m, 4H), 1.77 – 1.67 (m, 4H), 1.67 – 1.61 (m, 1H), 1.27 (qt, *J* = 12.8, 3.8 Hz, 2H), 1.16 (tt, *J* = 12.4, 3.2 Hz, 1H), 1.08 (qd, *J* = 13.7, 12.8, 3.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.59, 140.67, 128.54, 127.03, 126.23, 123.89, 61.64, 54.29, 42.93, 40.63, 33.60, 33.08, 26.35, 26.20. HRMS (ESI) m/z calc'd for $C_{20}H_{19}NO_3$ $[M+H]^+$: 284.378; found 284.2379.

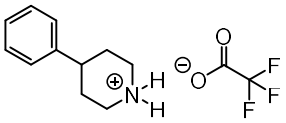
Scheme 2.1: General 4-phenylpiperidine complex formation



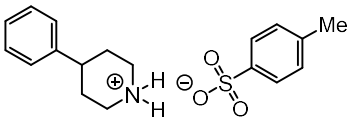
A solution of 4-phenylpiperidine (806.3 mg, 5 mmol, 1 eq) in DCM (0.25 M) was cooled to 0 °C and either BF_3•OEt_2 (1.1 eq) or Bronsted acid (1 eq) was added. After stirring for 30 min at 0 °C, the solution warmed to room temperature and stirred for one hour. The solution was then concentrated under reduced pressure and purified *via* trituration with Et_2O, recrystallization, or flash column chromatography.



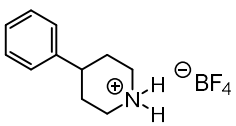
4-phenylpiperidine-borontrifluoride: BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. equivalent) was used in the general 4-phenylpiperidine complexation procedure. The crude complex was purified by column chromatography (25% → 50% → 75% EtOAc/Hx) to afford 4-phenylpiperidine-borontrifluoride as a white solid (1.10 g, 4.8 mmol, 96% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (app t, *J* = 7.6 Hz, 2H), 7.26 (app t, *J* = 7.4 Hz, 1H), 7.20 (app d, *J* = 7.5 Hz, 2H), 3.58 (app d, *J* = 13.6 Hz, 2H), 3.46 (br s, 1H), 2.95 (qd, *J* = 13.6, 2.8 Hz, 2H), 2.80 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.15 (d, *J* = 13.4 Hz, 2H), 1.78 (qd, *J* = 13.4, 3.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.64, 129.00, 127.25, 126.62, 46.25, 40.85, 32.25. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.82 (q, *J* = 14.9 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{11}H_{14}BNF_3$ $[M-H]^-$: 228.1171; found 228.1173.



4-phenylpiperidin-1-ium trifluoroacetate: Trifluoroacetic acid (0.39 mL, 5 mmol, 1 eq) was used in the general 4-phenylpiperidine complexation procedure. The crude salt was triturated with Et_2O to afford 4-phenylpiperidin-1-ium trifluoroacetate as a white solid (1.27 g, 4.6 mmol, 92% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (br s, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.26 – 7.21 (m, 3H), 3.38 (app d, J = 12.4 Hz, 2H), 3.01 (td, J = 12.9, 3.0 Hz, 2H), 2.84 (tt, J = 12.2, 3.7 Hz, 1H), 1.93 (app d, J = 14.4 Hz, 2H), 1.80 (app q, J = 13.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 158.40 (q, J = 31.1 Hz), 144.65, 128.59, 126.54, 126.49, 117.22 (q, J = 299.8 Hz), 43.60, 38.95, 29.46. ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.43. HRMS (ESI) m/z calc'd for $C_{11}H_{16}N$ $[M\text{-}TFA+H]^+$: 162.1283; found 162.1276.



4-phenylpiperidin-1-ium tosylate: *p*-Toluenesulfonic acid monohydrate (951.1 mg, 5 mmol, 1 eq) was used in the general 4-phenylpiperidine complexation procedure. The crude salt was triturated with Et_2O to afford 4-phenylpiperidin-1-ium tosylate as a white solid (1.65 g, 4.94 mmol, 99% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (br s, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.27 – 7.19 (m, 3H), 7.13 (d, J = 7.8 Hz, 2H), 3.37 (app d, J = 12.5 Hz, 2H), 3.00 (td, J = 12.9, 3.0 Hz, 2H), 2.83 (tt, J = 12.3, 3.7 Hz, 1H), 2.29 (s, 3H), 1.91 (app d, J = 13.6 Hz, 2H), 1.78 (qd, J = 13.3, 4.0 Hz, 2H) ^{13}C NMR (126 MHz, DMSO) δ 145.50, 144.58, 137.75, 128.58, 128.10, 126.54, 126.48, 125.47, 43.69, 38.87, 29.44, 20.79. HRMS (ESI) m/z calc'd for $C_{11}H_{16}N$ $[M\text{-}TsOH+H]^+$: 162.1283; found 162.1275



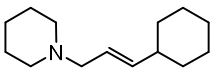
4-phenylpiperidin-1-ium tetrafluoroborate: Tetrafluoroboric acid diethyl ether complex (0.69 mL, 5 mmol, 1 eq) was used in the general 4-

phenylpiperidine complexation procedure. The crude solid was recrystallized from Acetone/Et_2O to afford 4-phenylpiperidin-1-ium tetrafluoroborate as a white solid (914.8 mg, 3.7 mmol, 74% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.19 (m, 3H), 7.01 (br s, 1H), 6.56 (br s, 1H), 3.72 (app d, *J* = 12.7 Hz, 2H), 3.27 – 3.14 (m, 2H), 2.80 (tt, *J* = 10.5, 5.5 Hz, 1H), 2.16 – 2.00 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.37, 128.97, 127.25, 126.78, 45.97, 40.24, 29.89. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -150.03, -150.09. *Note: minor singlet comes from natural minor ^{10}B isotope.* HRMS (ESI) m/z calc'd for $C_{11}H_{16}N$ $[M\text{-}BF_4]^+$: 162.1283; found 162.1276.

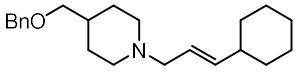
2.4.3 Simple Substrate Scope

General Allylic C—H Amination Procedure:

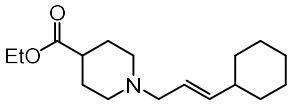
To a ½ dram vial with stir bar was added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq) Ma-SOX (6.9 mg, 0.02 mmol, 0.1 eq), amine nucleophile (0.2 mmol, 1 eq) and 2,5 dimethylbenzoquinone (30 mg, 0.22 mmol, 1.1 eq). A fresh solution of dibutyl phosphate in solvent was added (0.2 mL), then allyl cyclohexane (31 μL, 0.2 mmol, 1 eq). The vial was sealed with Teflon tape and parafilm to prevent any liquid from escaping, then placed in a 45 °C aluminium block. The vial was stirred at 45 °C for 48—72 h. Unless otherwise indicated, the crude mixture was subjected to the following aqueous workup: The crude mixture was diluted with 25 mL of EtOAc and washed with 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO_3$, then 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO_3$, then 5 mL of 1 M NaOH, then 5 mL of sat. $NaHSO_3$, then 5 mL of 1 M NaOH (7 washes in total). The crude product was then dried with Na_2SO_4. Finally, the product was purified *via* flash column chromatography.



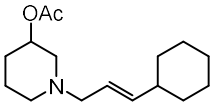
(E)-1-(3-cyclohexylallyl)piperidine (4): Piperidine-borontrifluoride (30.6 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutyl phosphate in dioxane (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 23.3 mg, 56% yield; Run 2: 22.2 mg, 54% yield; Run 3: 23.4 mg, 56% yield. **Average 55% yield (±1.6%)**. Spectral data were in accordance to literature values.



(E)-4-((benzyloxy)methyl)-1-(3-cyclohexylallyl)piperidine (5): 4-((benzyloxy)methyl)piperidine-borontrifluoride (54.6 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→15% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 47.8 mg, 73% yield; Run 2: 48.1 mg, 73% yield; Run 3: 48.1 mg, 73% yield. **Average 73% yield (±1.4%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 4H), 7.29 – 7.24 (m, 1H), 5.53 (dd, *J* = 15.5, 6.3 Hz, 1H), 5.44 (dt, *J* = 15.3, 6.4 Hz, 1H), 4.49 (s, 2H), 3.32 (d, *J* = 6.6 Hz, 2H), 3.02 – 2.83 (m, 4H), 1.98 – 1.88 (m, 1H), 1.92 (td, *J* = 11.9, 2.7 Hz, 2H), 1.77 (app d, *J* = 12.7 Hz, 2H), 1.74 – 1.67 (m, 4H), 1.67 – 1.60 (m, 2H), 1.32 (qd, *J* = 12.2, 3.8 Hz, 2H), 1.28 – 1.20 (m, 2H), 1.15 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.11 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 141.02, 138.70, 128.43, 127.62, 127.58, 123.35, 75.48, 73.16, 61.36, 53.23, 40.57, 36.28, 33.00, 29.15, 26.29, 26.13. HRMS (ESI) m/z calc'd for $C_{22}H_{34}NO$ $[M+H]^+$: 328.2640; found 328.2628.

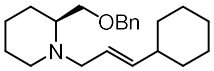


ethyl (E)-1-(3-cyclohexylallyl)piperidine-4-carboxylate (6): ethyl piperidine-4-carboxylate-borontrifluoride (45 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→15% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 47.1 mg, 84% yield; Run 2: 46.5 mg, 83% yield; Run 3: 45.6mg, 83% yield. **Average 83% yield (±1.4%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.52 (dd, *J* = 16.1, 6.7 Hz, 1H), 5.42 (dtd, *J* = 15.4, 6.5, 1.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.90 (d, *J* = 6.7 Hz, 2H), 2.89 – 2.84 (m, 2H), 2.26 (tt, *J* = 11.0, 4.1 Hz, 1H), 1.99 – 1.84 (m, 5H), 1.76 (td, *J* = 11.3, 3.5 Hz, 2H), 1.73 – 1.67 (m, 4H), 1.67 – 1.61 (m, 1H), 1.32 – 1.19 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.15 (tt, *J* = 12.4, 3.0 Hz, jjj1H), 1.11 – 1.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.31, 140.61, 123.86, 61.50, 60.39, 52.96, 41.41, 40.60, 33.08, 28.43, 26.34, 26.19, 14.37. HRMS (ESI) m/z calc'd for $C_{17}H_{30}NO_2$ $[M+H]^+$: 280.2277; found 280.2273.

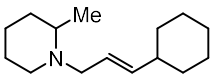


(E)-1-(3-cyclohexylallyl)piperidin-3-yl acetate (7): piperidin-3-yl acetate-borontrifluoride (42.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→2%→5%→10% EtOAc/Hx as an eluent) afforded the product as a yellow oil. Run 1: 43.4 mg, 82% yield; Run 2: 41.5 mg, 78% yield; Run 3: 41.8 mg, 79% yield. **Average 80% yield (±2.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.51 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.41 (dt, *J* = 15.8, 6.9, 5.8 Hz, 1H), 4.86 (tt, *J* = 7.9, 3.9 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.91 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.69 (app d, *J* = 10.2 Hz, 1H), 2.58 –

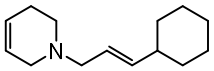
2.49 (m, 1H), 2.20 (app q, J = 10.7 Hz, 2H), 2.05 (s, 3H), 1.99 – 1.89 (m, 1H), 1.88 – 1.80 (m, 1H), 1.79 – 1.73 (m, 1H), 1.73 – 1.67 (m, 4H), 1.66 – 1.52 (m, 2H), 1.48 – 1.38 (m, 1H), 1.31 – 1.19 (m, 2H), 1.15 (tt, J = 12.2, 3.0 Hz, 1H), 1.11 – 1.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.64, 140.77, 123.45, 69.82, 61.29, 56.87, 53.32, 40.60, 33.06, 29.60, 26.32, 26.17, 22.77, 21.53. HRMS (ESI) m/z calc'd for $C_{16}H_{28}NO_2$ $[M+H]^+$: 266.2120; found 266.2110.



(*S*,*E*)-2-((benzyloxy)methyl)-1-(3-cyclohexylallyl)piperidine (8): (*S*)-2-((benzyloxy)methyl)piperidine-borontrifluoride (54.6 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.25M solution of dibutylphosphate in toluene (0.25 eq) as a solvent and stirred for 72 h. . Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→2%→5%→10% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 43.2 mg, 66% yield; Run 2: 43.4 mg, 66% yield; Run 3: 44.0 mg, 67% yield. **Average 66% yield (±0.6%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (app d, J = 4.4 Hz, 4H), 7.30 – 7.25 (m, 1H), 5.50 – 5.43 (m, 2H), 4.53 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 12.3 Hz, 1H), 3.54 (dd, J = 9.8, 4.1 Hz, 1H), 3.46 (dd, J = 9.8, 4.9 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.01 – 2.93 (m, 1H), 2.86 (dt, J = 117, 3.9 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.11 (td, J = 11.2, 3.3 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.75 – 1.66 (m, 6H), 1.66 – 1.60 (m, 1H), 1.61 – 1.43 (m, 3H), 1.34 – 1.19 (m, 3H), 1.15 (tt, J = 12.4, 2.9 Hz, 1H), 1.11 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.25, 138.57, 128.45, 127.87, 127.65, 123.50, 73.35, 72.34, 60.45, 56.83, 52.50, 40.67, 33.14, 29.99, 26.36, 26.20, 25.77, 24.09. HRMS (ESI) m/z calc'd for $C_{22}H_{34}NO$ $[M+H]^+$: 328.2640; found 328.2628. $[\alpha]^{22}_D$ = -43.34 (c = 1.15, $CHCl_3$).

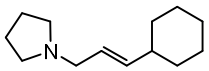


(E)-1-(3-cyclohexylallyl)-2-methylpiperidine (9): 2-methylpiperidine-borontrifluoride (33.4 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→0.5→1→2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 23.8 mg, 54% yield; Run 2: 22.5 mg, 51% yield; Run 3: 23.4 mg, 53% yield. **Average 52% yield (±1.4%)**. ^{1}H NMR (499 MHz, Chloroform-*d*) δ 5.58 – 5.38 (m, 2H), 3.32 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.93 – 2.78 (m, 2H), 2.24 – 2.17 (m, 1H), 2.04 (td, *J* = 11.4, 3.0 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.75 – 1.66 (m, 4H), 1.66 – 1.55 (m, 4H), 1.55 – 1.45 (m, 1H), 1.32 – 1.19 (m, 4H), 1.14 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.11 – 0.98 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.33, 123.27, 56.65, 56.01, 52.26, 40.72, 34.94, 33.17, 33.15, 26.36, 26.31, 26.21, 24.36, 19.45. HRMS (ESI) m/z calc'd for $C_{15}H_{28}N$ $[M+H]^+$: 222.2222; found 222.2220.

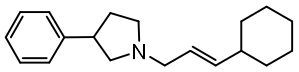


(E)-1-(3-cyclohexylallyl)-1,2,3,6-tetrahydropyridine (10): 1,2,3,6-tetrahydropyridine-borontrifluoride (30.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.25 eq) as a solvent and stirred for 48. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→5% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 24.4 mg, 59% yield; Run 2: 25.3 mg, 62% yield; Run 3: 26.0 mg, 63% yield. **Average 61% yield (± 2.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.74 (dtt, *J* = 9.3, 3.6, 2.1 Hz, 1H), 5.66 (dtt, *J* = 10.0, 3.4, 1.9 Hz, 1H), 5.55 (dd, *J* = 15.5, 6.2 Hz, 1H), 5.47 (dt, *J* = 16.1, 6.4 Hz, 1H), 3.00 (d, *J* = 6.4 Hz, 2H), 2.94 (app p, *J* = 2.6 Hz, 2H), 2.54 (t, *J* = 5.7 Hz, 2H), 2.22

– 2.14 (m, 2H), 1.99 – 1.90 (m, 1H), 1.75 – 1.66 (m, 4H), 1.67 – 1.59 (m, 1H), 1.32 – 1.19 (m, 2H), 1.16 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.12 – 1.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.55, 125.48, 125.37, 123.93, 61.04, 52.64, 49.64, 40.62, 33.09, 26.35, 26.30, 26.19. HRMS (ESI) m/z calc'd for $C_{14}H_{24}N$ $[M+H]^+$: 206.1909; found 206.1910.

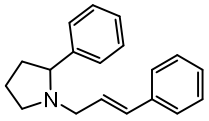


(E)-1-(3-cyclohexylallyl)piperidine (11): Pyrrolidine-borontrifluoride (27.8 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 1.2 mL of a 0.0833 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 14.0 mg, 36% yield; Run 2: 13.7 mg, 35% yield; Run 3: 13.9 mg, 36% yield. **Average 36% yield (±0.4%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.60 – 5.42 (m, 2H), 3.02 (d, *J* = 5.9 Hz, 2H), 2.52 – 2.39 (m, 4H), 1.98 – 1.89 (m, 1H), 1.82 – 1.74 (m, 4H), 1.74 – 1.66 (m, 4H), 1.66 – 1.60 (m, 1H), 1.32 – 1.20 (m, 2H), 1.15 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.11 – 1.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.39, 124.93, 58.60, 54.00, 40.57, 33.07, 26.36, 26.20, 23.54. HRMS (ESI) m/z calc'd for $C_{13}H_{24}N$ $[M+H]^+$: 194.1909; found 194.1900.

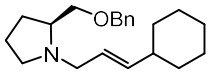


(E)-1-(3-cyclohexylallyl)-3-phenylpyrrolidine (12): 3-phenylpyrrolidine-borontrifluoride (43 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 33.0 mg, 61% yield; Run 2: 33.6 mg, 62% yield; Run 3: 34.1 mg,

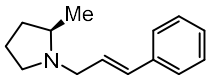
63% yield. **Average 62% yield (±1.1)** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 4H), 7.19 (tt, *J* = 6.8, 1.8 Hz, 1H), 5.57 (dd, *J* = 15.5, 6.0 Hz, 1H), 5.51 (dt, *J* = 15.4, 6.0 Hz, 1H), 3.37 (p, *J* = 7.9 Hz, 1H), 3.15 – 3.04 (m, 3H), 2.89 (ddd, *J* = 9.3, 7.9, 5.6 Hz, 1H), 2.59 (app td, *J* = 9.0, 6.3 Hz, 1H), 2.41 (t, *J* = 8.9 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.00 – 1.83 (m, 2H), 1.76 – 1.66 (m, 4H), 1.66 – 1.60 (m, 1H), 1.32 – 1.20 (m, 2H), 1.15 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.11 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.43, 139.59, 128.52, 127.49, 126.20, 124.74, 62.21, 58.72, 54.56, 43.58, 40.60, 33.31, 33.09, 26.35, 26.20. HRMS (ESI) m/z calc'd for $C_{19}H_{28}N$ $[M+H]^+$: 270.2222; found 270.2232.



1-cinnamyl-2-phenylpyrrolidine (13): 2-phenylpyrrolidine-borontrifluoride (43 mg, 0.2 mmol, 1 eq) and allylbenzene (23.6 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→0.5%→1% EtOAc/Hx as an eluent) afforded the product as a yellow oil. Run 1: 42.4 mg, 81% yield; Run 2: 45.0 mg, 85% yield; Run 3: 44.1 mg, 85% yield. **Average 84% yield (±2.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.31 (m, 4H), 7.31 – 7.26 (m, 2H), 7.26 – 7.23 (m, 3H), 7.22 – 7.18 (m, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.25 (ddd, *J* = 15.8, 8.0, 5.3 Hz, 1H), 3.42 (ddd, *J* = 13.5, 5.3, 1.7 Hz, 1H), 3.37 – 3.28 (m, 2H), 2.80 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.31 (q, *J* = 8.9 Hz, 1H), 2.26 – 2.14 (m, 1H), 2.01 – 1.90 (m, 1H), 1.86 – 1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.72, 137.41, 131.70, 128.59, 128.53, 128.13, 127.72, 127.32, 127.14, 126.38, 69.69, 56.35, 53.94, 35.13, 22.55. HRMS (ESI) m/z calc'd for $C_{19}H_{22}N$ $[M+H]^+$: 264.1752; found 264.1741.

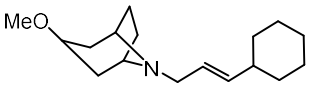


(*S*,*E*)-2-((benzyloxy)methyl)-1-(3-cyclohexylallyl)pyrrolidine (14): (S)-2-((benzyloxy)methyl)pyrrolidine-borontrifluoride (51.8 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.25 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→2% EtOAc/Hx as an eluent) afforded the product as a yellow oil. Run 1: 42.3 mg, 67% yield; Run 2: 44.2 mg, 71% yield; Run 3: 43.2 mg, 69% yield. **Average 69% yield (±1.6%)**.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (app d, *J* = 4.4 Hz, 4H), 7.29 – 7.24 (m, 1H), 5.56 – 5.42 (m, 2H), 4.52 (s, 2H), 3.52 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.45 (dd, *J* = 13.3, 5.3 Hz, 1H), 3.35 (dd, *J* = 9.3, 6.5 Hz, 1H), 3.06 (ddd, *J* = 9.4, 6.9, 2.4 Hz, 1H), 2.88 (dd, *J* = 12.8, 6.5 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.21 (td, *J* = 9.5, 7.1 Hz, 1H), 1.97 – 1.86 (m, 2H), 1.79 – 1.59 (m, 8H), 1.32 – 1.19 (m, 2H), 1.15 (tt, *J* = 12.5, 3.0 Hz, 1H), 1.11 – 0.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.49, 138.68, 128.44, 127.78, 127.60, 124.90, 73.94, 73.43, 62.77, 57.79, 54.57, 40.53, 33.04, 28.90, 26.36, 26.20, 22.94. HRMS (ESI) m/z calc'd for $C_{21}H_{32}NO$ $[M+H]^+$: 314.2484; found 314.2473. $[\alpha]^{22}_D$ = -52.22 (c = 1.26, $CHCl_3$).

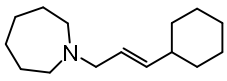


(*R*)-1-cinnamyl-2-methylpyrrolidine (15): (*S*)-2-methylpyrrolidine-borontrifluoride (30.6 mg, 0.2 mmol, 1 eq) and allylbenzene (23.6 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→5% EtOAc/Hx as an eluent) afforded the product as a yellow oil. Run 1: 22.7 mg, 56% yield; Run 2: 23.5 mg, 58% yield; Run 3: 23.0 mg, 57% yield. **Average 57% yield (±1.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (app d, *J* =

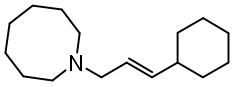
7.4 Hz, 2H), 7.30 (app t, *J* = 7.6 Hz, 2H), 7.21 (app t, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.35 (ddd, *J* = 15.7, 7.9, 5.6 Hz, 1H), 3.63 (ddd, *J* = 13.2, 5.6, 1.6 Hz, 1H), 3.14 (ddd, *J* = 10.2, 8.2, 2.6 Hz, 1H), 2.87 (dd, *J* = 13.2, 7.9 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.18 (q, *J* = 9.1 Hz, 1H), 2.00 – 1.90 (m, 1H), 1.84 – 1.72 (m, 1H), 1.72 – 1.62 (m, 1H), 1.52 – 1.41 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.34, 131.92, 128.64, 128.12, 127.39, 126.39, 59.67, 56.36, 54.36, 32.94, 21.69, 19.23. HRMS (ESI) m/z calc'd for $C_{14}H_{20}N$ $[M+H]^+$: 202.1596; found 202.1589. $[\alpha]^{22}_D$ = -115.73 (c = 1.19, $CHCl_3$).



(1R,5S)-8-((E)-3-cyclohexylallyl)-3-methoxy-8-azabicyclo[3.2.1]octane (16): (1R,5S)-3-methoxy-8-azabicyclo[3.2.1]octane-borontrifluoride (41.8 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 34.1 mg, 65% yield; Run 2: 32.6 mg, 62% yield; Run 3: 32.2 mg, 61% yield. **Average 63% yield (±1.9%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.64 – 5.41 (m, 2H), 3.41 (t, *J* = 5.1 Hz, 1H), 3.31 – 3.24 (m, 2H), 3.23 (s, 3H), 2.99 (d, *J* = 4.8 Hz, 2H), 2.10 – 2.01 (m, 2H), 2.02 – 1.91 (m, 3H) 1.89 – 1.80 (m, 4H), 1.75 – 1.66 (m, 4H), 1.66 – 1.58 (m, 1H), 1.30 – 1.18 (m, 2H), 1.14 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.10 – 0.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.11, 123.54, 74.17, 58.04, 56.36, 54.78, 40.55, 35.26, 32.98, 26.27, 26.11, 25.75. HRMS (ESI) m/z calc'd for $C_{17}H_{30}NO$ $[M+H]^+$: 264.2327; found 264.2328.

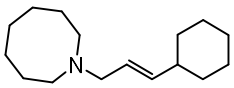


(E)-1-(3-cyclohexylallyl)azepane (17): Azepane-borontrifluoride (33.4 mg, 0.2 mmol, 1 eq) and allylcyclohexane were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutyl phosphate in dioxane (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 33.9 mg, 77% yield; Run 2: 31.9 mg, 72% yield; Run 3: 33.9mg, 77% yield. **Average 75% yield (±2.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.51 (dd, *J* = 15.6, 5.7 Hz, 1H), 5.46 (dt, *J* = 15.5, 5.9 Hz, 1H), 3.06 (d, *J* = 5.8 Hz, 2H), 2.68 – 2.51 (m, 4H), 2.01 – 1.89 (m, 1H), 1.77 – 1.54 (m, 13H), 1.32 – 1.20 (m, 2H), 1.16 (tt, *J* = 12.5, 3.0 Hz, 1H), 1.11 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.15, 124.61, 61.00, 55.46, 40.61, 33.13, 27.82, 27.06, 26.35, 26.19. HRMS (ESI) m/z calc'd for $C_{15}H_{28}N$ $[M+H]^+$: 222.2222; found 222.2220.

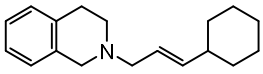


(E)-1-(3-cyclohexylallyl)azocane (18): Azocane-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5% EtOAc/Hx eluent) afforded the product as a yellow oil Run 1: 36.4 mg, 77% yield; Run 2: 36.4 mg, 77% yield; Run 3: 37.3mg, 79% yield. **Average 78% yield (±1.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.48 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.42 (dt, *J* = 15.5, 6.0 Hz, 1H), 3.01 (d, *J* = 5.9 Hz, 2H), 2.53 (t, *J* = 5.2 Hz, 4H), 1.93 – 1.85 (m, 1H), 1.77 – 1.67 (m, 4H), 1.66 – 1.48 (m, 11H), 1.32 – 1.21 (m, 2H), 1.16 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.12 – 1.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.93, 126.00, 61.23, 53.48, 40.60, 33.24, 27.88,

27.57, 26.49, 26.38, 26.23. HRMS (ESI) m/z calc'd for $C_{16}H_{30}N$ $[M+H]^+$: 236.2378; found 236.2378.

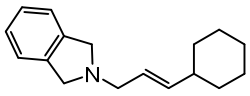


(E)-1-(3-cyclohexylallyl)azocane (18): Azocane-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 26.4 mg, 56% yield; Run 2: 25.2 mg, 53% yield; Run 3: 25.0 mg, 53% yield. **Average 54% yield (±1.7%)**.

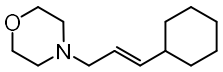


(E)-2-(3-cyclohexylallyl)-1,2,3,4-tetrahydroisoquinoline (19): 1,2,3,4-tetrahydroisoquinoline-borontrifluoride (80.4 mg, 0.4 mmol, 1 eq) and allylcyclohexane (49.7 mg, 0.4 mmol, 1 eq) were reacted according to general procedure using 0.4 mL of a 0.5 M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 70.3 mg, 69% yield; Run 2: 71.4 mg, 70% yield; Run 3: 70.4 mg, 69% yield. **Average 69% yield (± 0.6%)**. ^{1}H NMR (499 MHz, Chloroform-*d*) δ 7.17 – 7.11 (m, 3H), 7.08 – 7.03 (m, 1H), 5.65 (dd, *J* = 15.4, 6.4 Hz, 1H), 5.56 (dtd, *J* = 15.4, 6.5, 1.1 Hz, 1H), 3.64 (s, 2H), 3.15 (d, *J* = 6.4 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.08 – 1.98 (m, 1H), 1.83 – 1.72 (m, 4H), 1.72 – 1.61 (m, 1H), 1.38 – 1.26 (m, 2H), 1.21 (tt, *J* = 12.4, 3.2 Hz, 1H), 1.18 – 1.07 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.72, 135.00, 134.47, 128.76, 126.73,

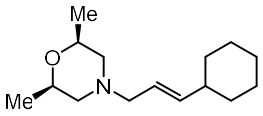
126.17, 125.64, 123.89, 60.91, 56.05, 50.58, 40.63, 33.10, 29.22, 26.34, 26.19. HRMS (ESI) m/z calc'd for $C_{18}H_{26}N$ $[M+H]^+$: 256.2065; found 256.2052.



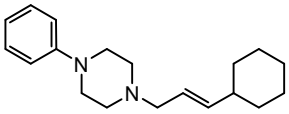
(E)-2-(3-cyclohexylallyl)isoindoline (20): Isoindoline-borontrifluoride (37.4 mg, 0.2 mmol, 1 eq) and allyllcyclohexane (25 mg, 0.2 mmol, 1 eq), were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 32.5 mg, 68% yield; Run 2: 32.3 mg, 67% yield; Run 3: 31.4 mg, 65% yield. **Average 67% yield (±1.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.21 – 7.16 (m, 4H), 5.65 (dd, *J* = 15.4, 6.4 Hz, 1H), 5.55 (dt, *J* = 15.5, 6.6 Hz, 1H), 3.91 (s, 4H), 3.31 (d, *J* = 6.3 Hz, 2H), 2.05 – 1.90 (m, 1H), 1.81 – 1.69 (m, 4H), 1.69 – 1.63 (m, 1H), 1.28 (qt, *J* = 12.1, 3.5 Hz, 2H), 1.18 (tt, *J* = 12.4, 3.2 Hz, 1H), 1.14 – 1.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.40, 139.85, 126.74, 124.69, 122.42, 58.79, 58.27, 40.63, 33.12, 26.36, 26.21. HRMS (ESI) m/z calc'd for $C_{17}H_{24}N$ $[M+H]^+$: 242.1909; found 242.1897 .



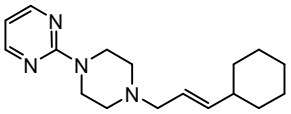
(E)-4-(3-cyclohexylallyl)morpholine (21): morpholine-borontrifluoride (31.0 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 32.1 mg, 77% yield; Run 2: 30.9 mg, 74% yield; Run 3: 30.7 mg, 73% yield. **Average 75% yield (±1.8%)**. Spectral data were in accordance to literature values



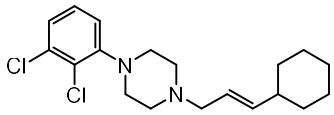
(2S,6R)-4-((E)-3-cyclohexylallyl)-2,6-dimethylmorpholine (22): (2S,6R)-2,6-dimethylmorpholine-borontrifluoride (36.6 mg, 0.2 mmol, 1 eq) was reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 hours . Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 39.7 mg, 84% yield; Run 2: 37.8 mg, 80% yield; Run 3: 38.1 mg, 80% yield. **Average 81% yield (±2.2%)**. Spectral data were in accordance to literature values



(E)-1-(3-cyclohexylallyl)-4-phenylpiperazine (23): 1-phenylpiperazine-borontrifluoride (46.0 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 h . Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→2→5% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 41.6 mg, 73% yield; Run 2: 42.3 mg, 74% yield; Run 3: 42.4 mg, 75% yield. **Average 74% yield (±0.8%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.85 (t, *J* = 7.1 Hz, 1H), 5.59 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.47 (dtd, *J* = 15.2, 6.7, 1.2 Hz, 1H), 3.24 – 3.20 (m, 4H), 3.00 (d, *J* = 6.7 Hz, 2H), 2.64 – 2.56 (m, 4H), 2.04 – 1.92 (m, 1H), 1.78 – 1.68 (m, 4H), 1.68 – 1.62 (m, 1H), 1.33 – 1.21 (m, 2H), 1.17 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.13 – 1.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.50, 141.08, 129.22, 123.47, 119.73, 116.15, 61.27, 53.15, 49.26, 40.64, 33.08, 26.34, 26.19. HRMS (ESI) m/z calc'd for $C_{19}H_{29}N_2$ $[M+H]^+$: 285.2331; found 285.2323.

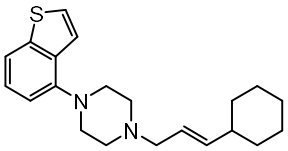


(*E*)-2-(4-(3-cyclohexylallyl)piperazin-1-yl)pyrimidine (24): 2-(piperazin-1-yl)pyrimidine-borontrifluoride (46.4 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) was reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography Brockmann Grade 3 alumina, 0→1→2→5% EtOAc/Hx eluent. Run 1: 33.1 mg, 58% yield; Run 2: 31.8 mg, 56% yield; Run 3: 32.5 mg, 57% yield. **Average 57% yield (±1.2%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 4.7 Hz, 2H), 6.47 (t, *J* = 4.7 Hz, 1H), 5.56 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.46 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.89 – 3.78 (m, 4H), 2.97 (d, *J* = 6.6 Hz, 2H), 2.48 (app t, *J* = 5.1 Hz, 4H), 2.01 – 1.91 (m, 1H), 1.76 – 1.67 (m, 4H), 1.67 – 1.60 (m, 1H), 1.32 – 1.21 (m, 2H), 1.16 (tt, *J* = 12.5, 3.1 Hz, 1H), 1.12 – 1.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.84, 157.83, 141.14, 123.39, 109.90, 61.38, 53.01, 43.83, 40.64, 33.06, 26.33, 26.18. HRMS (ESI) m/z calc'd for $C_{17}H_{27}N_4$ $[M+H]^+$: 287.2236; found 287.2235.

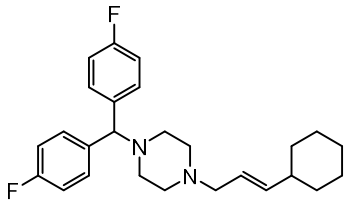


(E)-1-(3-cyclohexylallyl)-4-(2,3-dichlorophenyl)piperazine (25): 1-(2,3-dichlorophenyl)piperazine-borontrifluoride (59.8 mg, 0.2 mmol, 1eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→15% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 45.5 mg, 64% yield; Run 2: 47.5 mg, 67% yield; Run 3: 45.9 mg, 65% yield. **Average 65% yield (±1.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.10 (m, 2H), 6.96 (dd, *J* = 6.7, 2.9 Hz, 1H), 5.59 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.47 (dtd, *J* = 15.1, 6.7, 1.2 Hz, 1H), 3.07 (app br s, 4H), 3.02 (d, *J* = 6.7 Hz, 2H), 2.63

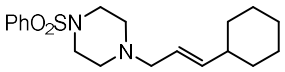
(app br s, 4H), 2.01 – 1.92 (m, 1H), 1.78 – 1.68 (m, 4H), 1.68 – 1.60 (m, 1H), 1.34 – 1.21 (m, 2H), 1.16 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.13 – 1.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.48, 141.13, 134.14, 127.65, 127.57, 124.64, 123.45, 118.75, 61.25, 53.23, 51.45, 40.65, 33.07, 26.33, 26.19. HRMS (ESI) m/z calc'd for $C_{19}H_{27}N_2Cl_2$ $[M+H]^+$: 353.1551; found 353.1555.



(E)-1-(benzo[b]thiophen-4-yl)-4-(3-cyclohexylallyl)piperazine (26): 1-(benzo[b]thiophen-4-yl)piperazine-borontrifluoride (57.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure 0.2 mL of an 0.25M solution of dibutyl phosphate in toluene (0.25 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→1→2%→3% EtOAc/Hx eluent) afforded the product as a yellow oil containing 5–6% of an inseparable olefin byproduct. Run 1: 43.6 mg, 64% yield; Run 2: 45.6 mg, 67% yield; Run 3: 42.9 mg, 63% yield. **Average 65% yield (±2.1%)**. Further purification using a 12g RediSepGold HP MPLC column (5% EtOAc/Hx eluent) afforded the pure product as a white solid (**54% yield**) with <1% olefinic impurity. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.38 (d, *J* = 5.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.61 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.50 (dt, *J* = 15.5, 6.7 Hz, 1H), 3.22 – 3.18 (m, 4H), 3.06 (d, *J* = 6.6 Hz, 2H), 2.71 – 2.68 (m, 4H), 2.06 – 1.94 (m, 1H), 1.77 – 1.69 (m, 4H), 1.68 – 1.62 (m, 1H), 1.35 – 1.22 (m, 2H), 1.18 (tt, *J* = 12.3, 3.2 Hz, 1H), 1.14 – 1.05 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.65, 141.22, 141.08, 134.20, 125.14, 125.00, 123.53, 122.05, 117.07, 112.30, 61.32, 53.49, 52.23, 40.64, 33.07, 26.32, 26.18. HRMS (ESI) m/z calc'd for $C_{18}H_{28}N_2S$ $[M+H]^+$: 341.2007; found 341.2049.

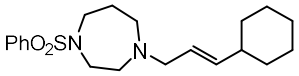


(E)-1-(bis(4-fluorophenyl)methyl)-4-(3-cyclohexylallyl)piperazine (27): 1-(bis(4-fluorophenyl)methyl)piperazine-borontrifluoride (71.4 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 h . Purification *via* flash column chromatography (Brockmann Grade 3 basic alumina, 0→5→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 66.5 mg, 81% yield; Run 2: 69.0 mg, 84% yield; Run 3: 67.7 mg, 83% yield. **Average 83% yield (±1.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 4H), 6.95 (t, *J* = 8.5 Hz, 4H), 5.52 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.41 (dt, *J* = 15.2, 7.1, 6.5 Hz, 1H), 4.21 (s, 1H), 2.93 (d, *J* = 6.6 Hz, 2H), 2.42 (app br s, 8H), 1.97 – 1.87 (m, 1H), 1.73 – 1.59 (m, 5H), 1.31 – 1.19 (m, 2H), 1.14 (tt, *J* = 12.6, 3.0 Hz, 1H), 1.10 – 0.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) 161.90 (d, J = 245.5 Hz), 140.88, 138.43 (d, J = 3.0 Hz), 129.39 (d, J = 7.9 Hz), 123.54, 115.46 (d, J = 21.2 Hz), 74.62, 61.16, 53.32, 51.85, 40.59, 33.05, 26.31, 26.14. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -115.69 (p, *J* = 7.2 Hz). HRMS (ESI) m/z calc'd for $C_{26}H_{33}N_2F_2$ $[M+H]^+$: 411.2612; found 411.2615.

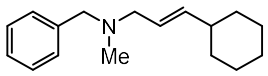


(E)-1-(3-cyclohexylallyl)-4-(phenylsulfonyl)piperazine (28): 1-(phenylsulfonyl)piperazine-borontrifluoride (117.4 mg, 0.4 mmol, 1 eq) and allylcyclohexane (49.7 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.4 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 5→15% EtOAc/Hx eluent) afforded a yellow solid which was further recrystallized from hot ethanol to afford the product as a pale yellow solid. Run 1: 78.4 mg, 56% yield; Run 2: 74.6 mg, 53% yield; Run 3: 81.8 mg, 58% yield.

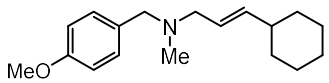
Average 56% yield (±2.5 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (app d, *J* = 7.3 Hz, 2H), 7.58 (app t, *J* = 7.5 Hz, 1H), 7.52 (app t, *J* = 7.8 Hz, 2H), 5.52 (dd, *J* = 15.4, 6.5 Hz, 1H), 5.30 (dtd, *J* = 15.2, 6.8, 1.4 Hz, 1H), 3.05–3.01 (m, 4H), 2.90 (d, *J* = 6.8 Hz, 2H), 2.49 (t, *J* = 5.0 Hz, 4H), 1.96 – 1.86 (m, 1H), 1.75–1.58 (m, 5H), 1.29 – 1.18 (m, 2H) 1.13 (tt, *J* = 12.5, 3.0 Hz, 1H), 1.09 – 0.98 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 141.63, 135.36, 132.92, 129.13, 128.00, 122.78, 60.70, 52.01, 46.21, 40.54, 32.96, 26.25, 26.10. HRMS (TOF MS ES+) m/z calc'd for $C_{19}H_{29}N_2O_2S$ $[M+H]^+$: 349.1905; found 349.1935.



(E)-1-(3-cyclohexylallyl)-4-(phenylsulfonyl)-1,4-diazepane (29): 1-(phenylsulfonyl)-1,4-diazepane-borontrifluoride (61.6 mg, 0.2 mmol, 2 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 53.5 mg, 74% yield; Run 2: 53.1 mg, 73% yield; Run 3: 53.5 mg, 74% yield. **Average 74% yield (±0.4%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 – 7.76 (m, 2H), 7.59 – 7.54 (m, 1H), 7.54 – 7.47 (m, 2H), 5.50 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.36 (dtd, *J* = 15.3, 7.1, 6.3, 1.0 Hz, 1H), 3.42 – 3.32 (m, 4H), 3.02 (d, *J* = 6.5 Hz, 2H), 2.68 – 2.65 (m, 2H), 2.64 – 2.61 (m, 2H), 2.00 – 1.88 (m, 1H), 1.81 (app p, *J* = 6.0 Hz, 2H), 1.76 – 1.60 (m, 5H), 1.25 (qt, *J* = 12.7, 3.4 Hz, 2H), 1.15 (tt, *J* = 12.5, 3.1 Hz, 1H), 1.10 – 0.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.61, 139.19, 132.34, 129.03, 126.98, 123.92, 60.39, 55.68, 54.08, 48.32, 47.11, 40.45, 32.95, 27.90, 26.16, 26.01. HRMS (ESI) m/z calc'd for $C_{20}H_{31}N_2O_2S$ $[M+H]^+$: 363.2106; found 363.2116.

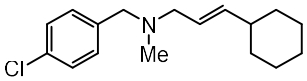


(*E*)-N-benzyl-3-cyclohexyl-N-methylprop-2-en-1-amine (30): N-methyl-1-phenylmethanamine-borontrifluoride (37.8 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 72 hours. Purification *via* the general workup procedure followed by flash column chromatography (Brockmann Grade 3 alumina, 0→1% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 28.5 mg, 59% yield; Run 2: 28.2 mg, 58% yield; Run 3: 29.6 mg, 61% yield. **Average 59% yield (±1.5)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 4.5 Hz, 4H), 7.27 – 7.21 (m, 1H), 5.55 (dd, *J* = 15.5, 6.2 Hz, 1H), 5.47 (dt, *J* = 15.9, 6.3, 5.8 Hz, 1H), 3.47 (s, 2H), 2.97 (d, *J* = 6.2 Hz, 2H), 2.17 (s, 3H), 2.01 – 1.92 (m, 1H), 1.76 – 1.67 (m, 4H), 1.67 – 1.61 (m, 1H), 1.34 – 1.21 (m, 2H), 1.16 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.13 – 1.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.42, 139.29, 129.30, 128.31, 127.01, 124.54, 61.67, 59.98, 42.14, 40.68, 33.15, 26.35, 26.20. HRMS (ESI) m/z calc'd for $C_{17}H_{26}N$ $[M+H]^+$: 244.2065; found 244.2069.

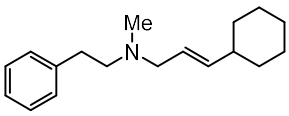


(E)-3-cyclohexyl-N-(4-methoxybenzyl)-N-methylprop-2-en-1-amine (31): 1-(4-methoxyphenyl)-N-methylmethanamine-borontrifluoride (43.8 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 72 hours. Purification *via* the general workup procedure followed by flash column chromatography (Brockmann Grade 3 alumina, 0→1→2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 37.5 mg, 69% yield; Run 2: 34.8 mg, 64% yield; Run 3: 36.1 mg, 66% yield. **Average 66% yield (±2.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.54 (dd, *J* = 15.6, 6.3 Hz, 1H),

5.46 (dt, *J* = 15.3, 6.4 Hz, 1H), 3.80 (s, 3H), 3.41 (s, 2H), 2.94 (d, *J* = 6.3 Hz, 2H), 2.15 (s, 3H), 2.01 – 1.91 (m, 1H), 1.77 – 1.67 (m, 4H), 1.67 – 1.59 (m, 1H), 1.34 – 1.21 (m, 2H), 1.16 (tt, *J* = 12.5, 3.1 Hz, 1H), 1.12 – 1.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.73, 140.38, 131.22, 130.45, 124.53, 113.69, 61.00, 59.76, 55.39, 41.96, 40.67, 33.14, 26.35, 26.19. HRMS (ESI) m/z calc'd for $C_{18}H_{28}NO$ $[M+H]^+$: 274.2171; found 274.2165.

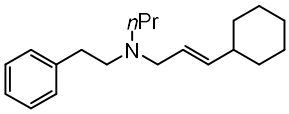


(*E*)-N-(4-chlorobenzyl)-3-cyclohexyl-*N*-methylprop-2-en-1-amine (32): 1-(4-chlorophenyl)-N-methylmethanamine-borontrifluoride (44.7 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M dibutylphosphate solution in toluene (0.5 eq) as a solvent and stirred for 72 hours. Purification *via* the general workup procedure followed by flash column chromatography (Brockmann Grade 3 alumina, 0→1→2% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 41.6 mg, 75% yield; Run 2: 41.8 mg, 75% yield; Run 3: 42.5 mg, 77% yield. **Average 76% yield (±0.9)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.22 (m, 4H), 5.54 (dd, *J* = 15.4, 6.4, 1H), 5.45 (dtd, *J* = 15.5, 6.4, 1.1 Hz, 1H), 3.42 (s, 2H), 2.95 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H), 2.01 – 1.91 (m, 1H), 1.79 – 1.68 (m, 4H), 1.67 – 1.56 (m, 1H), 1.33 – 1.21 (m, 2H), 1.15 (tt, *J* = 12.4, 2.7 Hz, 1H), 1.12 – 1.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.57, 137.92, 132.67, 130.51, 128.44, 124.32, 60.86, 59.92, 42.10, 40.67, 33.14, 26.33, 26.18. HRMS (ESI) m/z calc'd for $C_{17}H_{25}NCl$ $[M+H]^+$: 278.1676; found 278.1668.



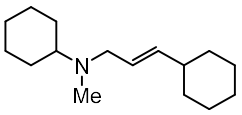
(*E*)-3-cyclohexyl-N-(4-methoxybenzyl)-N-methylprop-2-en-1-amine (33): 1-(4-methoxyphenyl)-N-methylmethanamine-borontrifluoride (40.6 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according

to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 72 hours. Purification *via* the general workup procedure and flash column chromatography (Brockmann Grade 3 alumina, 0→5→15% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 38.1 mg, 74% yield; Run 2: 38.5 mg, 75% yield; Run 3: 37.7 mg, 73% yield. **Average 74% yield (±0.8%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 5.55 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.45 (dtd, *J* = 16.0, 6.7, 0.9 Hz, 1H), 3.01 (d, *J* = 6.6 Hz, 2H), 2.85 – 2.73 (m, 2H), 2.68 – 2.56 (m, 2H), 2.29 (s, 3H), 2.01 – 1.92 (m, 1H), 1.76 – 1.68 (m, 4H), 1.68 – 1.61 (m, 1H), 1.36 – 1.21 (m, 2H), 1.17 (tt, *J* = 12.4, 3.1 Hz, 1H), 1.13 – 1.03 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.70, 140.46, 128.83, 128.49, 126.07, 124.17, 60.09, 59.07, 42.05, 40.64, 33.95, 33.11, 26.35, 26.19. HRMS (ESI) m/z calc'd for $C_{18}H_{28}NO_3$ $[M+H]^+$: 258.2222; found 258.2224.

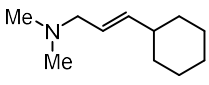


(*E*)-3-cyclohexyl-N-phenethyl-N-propylprop-2-en-1-amine (34): *N*-phenethylpropan-1-amine-borontrifluoride (46.2 mg, 0.2 mmol, 1 eq) and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent and stirred for 72 hours. Purification *via* the general workup procedure and flash column chromatography (Brockmann Grade 3 alumina, 0 →2 →5% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 30.0 mg, 53% yield; Run 2: 29.8 mg, 52% yield; Run 3: 32.5 mg, 57% yield. **Average 54% yield (±2.6%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 5.56 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.45 (dt, *J* = 15.3, 6.6 Hz, 1H), 3.12 (d, *J* = 6.5 Hz, 2H), 2.78 – 2.72 (m, 2H), 2.73 – 2.64 (m, 2H), 2.50 – 2.43 (m, 2H), 2.02 – 1.91 (m, 1H), 1.78 – 1.69 (m, 4H), 1.69 – 1.62 (m, 1H), 1.50 (h, *J* = 7.4 Hz, 2H), 1.34 – 1.22 (m, 2H), 1.17 (tt, *J* = 12.4, 3.0 Hz, 1H), 1.13 – 1.03 (m, 2H),

0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.04, 139.94, 128.85, 128.43, 125.95, 124.44, 56.50, 55.85, 55.61, 40.67, 33.35, 33.15, 26.35, 26.19, 20.42, 12.13. HRMS (ESI) m/z calc'd for $C_{20}H_{32}N$ $[M+H]^+$: 286.2535; found 286.2545.

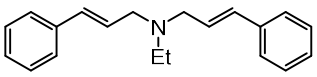


(E)-N-(3-cyclohexylallyl)-N-methylcyclohexanamine (35): N-methylcyclohexanamine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq), and allylcyclohexane (25 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.25 eq) as a solvent for and stirred 72 hours. Purification *via* the general workup procedure followed by flash column chromatography (Brockmann Grade 3 alumina, 0→1→2→5% EtOAc/Hx eluent) afforded the product as a brown oil. 1: 31.5 mg, 67% yield; Run 2: 32.4 mg, 69% yield; Run 3: 32.3 mg, 69% yield. **Average 68% yield (±1.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.49 (dd, J = 15.5, 6.3 Hz, 1H), 5.40 (dt, J = 15.7, 6.8, 6.2 Hz, 1H), 3.01 (d, J = 6.4 Hz, 2H), 2.43 – 2.32 (m, 1H), 2.19 (s, 3H), 2.00 – 1.89 (m, 1H), 1.84 – 1.73 (m, 4H), 1.73 – 1.66 (m, 4H), 1.66 – 1.57 (m, 2H), 1.31 – 1.13 (m, 7H), 1.13 – 1.02 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.49, 125.17, 61.83, 56.28, 40.48, 37.17, 32.98, 28.64, 26.41, 26.22, 26.05, 26.02. HRMS (ESI) m/z calc'd for $C_{16}H_{30}N$ $[M+H]^+$: 236.2378; found 236.2378.

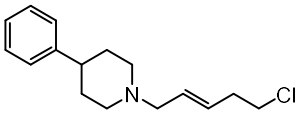


(E)-3-cyclohexyl-N,N-dimethylprop-2-en-1-amine (36): dimethylamine-borontrifluoride (33.9 eq, 0.3 mmol, 1.5 eq) was reacted according to general procedure using 0.5 mL of a 0.2 M dibutylphosphate solution in toluene (0.5 eq) as a solvent and stirred for 72 hours. The crude mixture was directly transferred to a 125mL erlenmeyer flask with 5 mL of Brockmann Grade 3 alumina and diluted with 10mL of EtOAc. Stir for 10 min at room

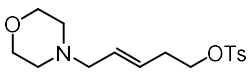
temperature. The crude mixture was then diluted with 15 mL of H_2O and 15 mL of Et_2O and transferred to a separatory funnel.. A 6M HCl solution (0.1 mL) in water was added. The aqueous layer was washed 3 times with diethyl ether. The aqueous layer was then basified by adding 15 mL of 1 M NaOH and diluted with 100 mL of EtOAc After separating the layers, the ethyl acetate layer was further washed 2 times with 1M NaOH (5mL). Finally, the ethyl acetate layer was dried *via* sodium sulfate. Further purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→2→5→10% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 10.3 mg, 31% yield; Run 2: 11.4 mg, 34% yield; Run 3: 12.2 mg, 36% yield. **Average 34% yield (±1.9)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.53 (dd, *J* = 15.4, 6.5 Hz, 1H), 5.42 (dt, *J* = 15.7, 6.7, Hz, 1H), 2.86 (d, *J* = 6.6 Hz, 2H), 2.21 (s, 6H), 2.01 – 1.89 (m, 1H), 1.77 – 1.68 (m, 4H), 1.67 – 1.60 (m, 1H), 1.36 – 1.19 (m, 2H), 1.15 (tt, *J* = 12.3, 2.8 Hz, 1H), 1.12 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.56, 124.29, 62.10, 45.06, 40.62, 33.09, 26.34, 26.18. HRMS (ESI) m/z calc'd for $C_{11}H_{22}N$ $[M+H]^+$: 168.1752; found 168.1745.



(E)-N-cinnamyl-N-ethyl-3-phenylprop-2-en-1-amine (37): ethanamine-borontrifluoride (11.3 mg, 0.1 mmol, 0.5 eq) was reacted according to the general procedure with allyl benzene (23.6 mg, 0.2 mmol, 1 eq) as the electrophile, using 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent and stirredfor 48 hours. Purification *via* the general workup procedure followed by flash column chromatography (Brockmann Grade 3 alumina, 10→75% DCM/Hx eluent) afforded the product as a yellow oil. Run 1: 22.6 mg, 81% yield; Run 2: 23.1 mg, 83% yield; Run 3: 22.7 mg, 82% yield. **Average 82% yield (±1.0%)**. Spectral data were in accordance to literature values

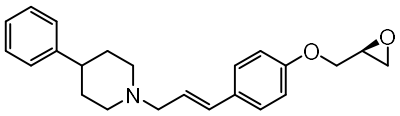


(*E*)-1-(5-chloropent-2-en-1-yl)-4-phenylpiperidine (38): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and 5-chloropent-1-ene (20.9 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (40 mL Brockmann Grade 3 alumina, Hx (200 mL)→2% EtOAc/Hx (200 mL)→4% EtOAc/Hx (200 mL)→6% EtOAc/Hx (200 mL) eluent) afforded the product as a coral-tinted oil. Run 1: 30.0 mg, 59% yield; Run 2: 28.5 mg, 55% yield; Run 3: 30.1 mg, 59% yield. **Average 57% yield (± 2.4%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (app t, *J* = 7.4 Hz, 2H), 7.23 (app d, *J* = 7.2 Hz, 2H), 7.19 (tt, *J* = 7.3, 1.3 Hz, 1H), 5.70 (dt, *J* = 15.4, 6.4 Hz, 1H), 5.63 (dt, *J* = 15.4, 6.2 Hz, 1H), 3.56 (t, *J* = 6.9 Hz, 2H), 3.11 – 3.04 (m, 2H), 3.02 (d, *J* = 6.3 Hz, 2H), 2.56 – 2.45 (m, 3H), 2.05 (td, *J* = 11.2, 4.1 Hz, 2H), 1.88 – 1.77 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.35, 129.92, 128.53, 126.97, 126.94, 126.26, 61.06, 54.27, 44.16, 42.73, 35.67, 33.45. HRMS (ES+) m/z calc'd for $C_{16}H_{23}NCl$ [M+H]+: 264.1519; found 264.1514.



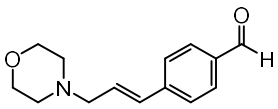
(*E*)-5-morpholinopent-3-en-1-yl 4-methylbenzenesulfonate (39): morpholine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 equiv) and pent-4-en-1-yl 4-methylbenzenesulfonate[1] (48.1 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using 0.2 mL of a 0.25 M solution of dibutyl phosphate in toluene (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2 deactivated with 4% triethylamine, 15% Acetone/Hx (600 mL)→20% Acetone/Hx (200 mL)→25% Acetone/Hx (200 mL)→30% Acetone/Hx (200 mL)→35% Acetone/Hx (200 mL)→40% Acetone/Hx (200 mL) eluent) afforded the product as a pink oil. Run 1: 44.9 mg, 69% yield; Run 2: 47.3 mg, 73%

yield; Run 3: 46.0 mg, 71% yield. **Average 71% yield (± 1.7%)**. The product readily decomposes and needs to be purified immediately to obtain the most optimal yields. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 (app d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.52 (dt, *J* = 15.5, 6.0 Hz, 1H), 5.46 (dt, *J* = 15.4, 6.0 Hz, 1H), 4.02 (t, *J* = 6.7 Hz, 2H), 3.67 (app t, *J* = 4.7 Hz, 4H), 2.88 (d, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 2.40 – 2.34 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.85, 133.19, 129.91, 128.35, 127.94, 69.58, 66.97, 61.00, 53.56, 31.99, 21.72. HSQC analysis confirms that 3 carbons (2 degenerate carbons on the aryl ring and 1 olefinic carbon) are observed at δ 129.91 ppm; please see spectra in the supporting information. HRMS (ES+) m/z calc'd for $C_{16}H_{24}NO_4S$ [M+H]+: 326.1426; found 326.1427.

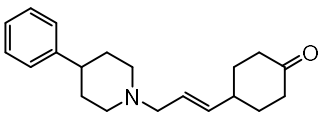


(*S*,*E*)-1-(3-(4-(oxiran-2-ylmethoxy)phenyl)allyl)-4-phenylpiperidine (40): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and (*S*)-2-((4-allylphenoxy)methyl)oxirane[2] (38.0 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. The crude mixture was diluted with 25 mL of EtOAc, stirred over 5 mL of Brockmann Grade 3 alumina for 15 minutes, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (50 mL SiO_2, 0.5% NH_4OH-MeOH/DCM (400 mL)→1% NH_4OH-MeOH/DCM (400 mL)→1.5% NH_4OH-MeOH/DCM (400 mL)→2% NH_4OH-MeOH/DCM (400 mL)→2.5% NH_4OH-MeOH/DCM (400 mL)→3.5% NH_4OH-MeOH/DCM (400 mL) eluent) afforded the product as a beige solid. Run 1: 35.6 mg, 51% yield; Run 2: 34.8 mg, 50% yield; Run 3: 36.1 mg, 52% yield. **Average 51% yield (± 1.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 (app d, *J* = 7.2 Hz, 2H), 7.22 – 7.18 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 15.8 Hz,

1H), 6.21 (dt, *J* = 15.7, 6.9 Hz, 1H), 4.22 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.95 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.24 (d, *J* = 6.9 Hz, 2H), 3.20 – 3.15 (m, 2H), 2.90 (app t, *J* = 4.5 Hz, 1H), 2.75 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.22 – 2.10 (m, 2H), 1.96 – 1.81 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.18, 146.11, 133.03, 130.24, 128.54, 127.68, 126.95, 126.31, 124.09, 114.82, 68.87, 61.47, 54.31, 50.20, 44.78, 42.57, 33.28. HRMS (ES+) m/z calc'd for $C_{23}H_{28}NO_2$ [M+H]+: 350.2120; found 350.2112. $[\alpha]^{24}_D$ = -3.3 (c = 0.95, MeOH).

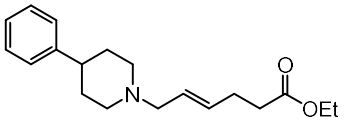


(E)-4-(3-morpholinoprop-1-en-1-yl)benzaldehyde (41): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 4-allylbenzaldehyde (29.2 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.25 M dibutylphosphate solution in toluene (0.5 eq) as a solvent for and stirred 48 hours. The crude mixture was filtered through a plug of celite and Brockmann Grade 3 alumina. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→3→5→10→20→30% EtOAc/Hx eluent) afforded the product as a yellow oil. 1: 40.6 mg, 88% yield; Run 2: 43.1 mg, 93% yield; Run 3: 41.5 mg, 89% yield. **Average 90% yield (±2.7%)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.98 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.8, 7.5 Hz, 1H), 3.84 – 3.67 (m, 4H), 3.20 (d, *J* = 6.6 Hz, 2H), 2.52 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.78, 142.95, 135.56, 132.29, 130.34, 130.30, 126.93, 67.09, 61.41, 53.89. HRMS (ESI) m/z calc'd for $C_{14}H_{118}NO_2$ [M+H]$^+$: 232.1338; found 232.1329.



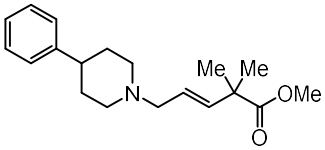
(*E*)-4-(3-(4-phenylpiperidin-1-yl)prop-1-en-1-yl)cyclohexan-1-one (42): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and 4-allylcyclohexane-1-one[3] (27.6 mg, 0.2 mmol, 1.0 eq) were reacted according to the general

procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. The crude mixture was diluted with 25 mL of EtOAc, stirred over 5 mL of Brockmann Grade 3 alumina for 15 minutes, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (50 mL SiO_2, 0.5% NH_4OH-MeOH/DCM (400 mL)→1% NH_4OH-MeOH/DCM (400 mL)→1.5% NH_4OH-MeOH/DCM (400 mL)→2% NH_4OH-MeOH/DCM (400 mL)→2.5% NH_4OH-MeOH/DCM (400 mL)→3% NH_4OH-MeOH/DCM (200 mL)→5% NH_4OH-MeOH/DCM (200 mL) eluent) afforded the product as a beige solid. Run 1: 42.9 mg, 72% yield; Run 2: 40.2 mg, 67% yield; Run 3: 40.1 mg, 67% yield. **Average 69% yield (± 2.9%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.23 (app d, *J* = 7.1 Hz, 2H), 7.19 (app t, *J* = 7.2 Hz, 1H), 5.71 – 5.62 (m, 2H), 3.17 – 3.11 (m, 2H), 3.11 – 3.07 (m, 2H), 2.58 – 2.45 (m, 2H), 2.44 – 2.32 (m, 4H), 2.17 – 2.10 (m, 2H), 2.10 – 2.04 (m, 2H), 1.93 – 1.82 (m, 4H), 1.62 (qd, *J* = 11.4, 5.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 211.37, 145.89, 138.05, 128.53, 126.89, 126.33, 125.16, 61.07, 54.13, 42.42, 40.56, 38.64, 33.07, 32.46. HRMS (ES+) m/z calc'd for $C_{20}H_{28}NO$ [M+H]+: 298.2171; found 298.2159.



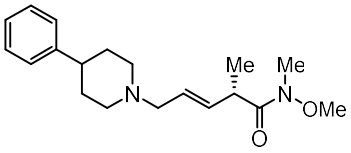
ethyl(*E*)-6-(4-phenylpieridin-1yl)hex-4-enoate (43): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and ethyl hex-5-enoate[4] (28.4 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2 deactivated with 4% triethylamine, 15% Acetone/Hx (800 mL)→60% Acetone/Hx (100 mL)→90% Acetone/Hx (200 mL) eluent) followed by a second flash column chromatography (50 mL SiO_2, DCM (200 mL)→1% MeOH/DCM (200 mL)→2% MeOH/DCM (200 mL)→3% MeOH/DCM (200

mL)→4% MeOH/DCM (200 mL)→5% MeOH/DCM (200 mL)→7% MeOH/DCM (200 mL) eluent) afforded the product as a pink/orange-tinted oil. Run 1: 44.1 mg, 62% yield; Run 2: 47.5 mg, 66% yield; Run 3: 47.6 mg, 67% yield. **Average 65% yield (± 2.7%).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (app t, *J* = 7.5 Hz, 2H), 7.24 (app d, *J* = 7.1 Hz, 2H), 7.21 (app t, *J* = 7.2 Hz, 1H), 5.75 – 5.60 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.20 – 3.13 (m, 2H), 3.10 (d, *J* = 5.8 Hz, 2H), 2.54 (tt, *J* = 11.8, 4.2 Hz, 1H), 2.47 – 2.36 (m, 4H), 2.16 (td, *J* = 11.7, 2.8 Hz, 2H), 2.00 – 1.83 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.06, 146.06, 133.10, 128.51, 126.98, 126.92, 126.29, 60.95, 60.43, 54.05, 42.54, 33.95, 33.14, 27.73, 14.33. HRMS (ES+) m/z calc'd for $C_{19}H_{28}NO_2$ [M+H]+: 302.2120; found 302.2125.

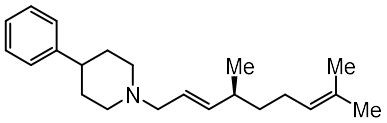


methyl (*E*)-2,2-dimethyl-5-(4-phenylpiperidin-1-yl)pent-3-enoate (44): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and methyl 2,2-dimethylpent-4-enoate[5] (28.4 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2 deactivated with 4% triethylamine, Hx (100 mL)→1% Acetone/Hx (200 mL)→2% Acetone/Hx (200 mL)→3% Acetone/Hx (200 mL)→4% Acetone/Hx (200 mL)→5% Acetone/Hx (200 mL)→6% Acetone/Hx (200 mL) eluent) afforded the product as a yellow-tinted oil. Run 1: 48.5 mg, 81% yield; Run 2: 48.3 mg, 81% yield; Run 3: 50.3 mg, 84% yield. **Average 82% yield (± 2.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (app t, *J* = 7.4 Hz, 2H), 7.22 (app d, *J* = 7.1 Hz, 2H), 7.18 (tt, *J* = 7.3, 1.3 Hz, 1H), 5.81 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.63 (dt, *J* = 15.6, 6.7 Hz, 1H), 3.66 (s, 3H), 3.06 – 3.00 (m, 4H), 2.48 (tt, *J* = 10.3, 4.9 Hz, 1H), 2.02 (td, *J* = 11.3, 3.5 Hz, 2H), 1.88 – 1.74 (m, 4H), 1.31 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-

d) δ 176.98, 146.38, 138.21, 128.49, 126.94, 126.21, 125.31, 61.23, 54.30, 52.14, 44.32, 42.75, 33.50, 25.21. HRMS (ES+) m/z calc'd for $C_{19}H_{28}NO_2$ [M+H]+: 302.2120; found 302.2114.

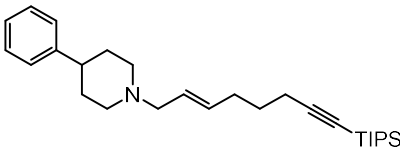


(*S*,*E*)-*N*-methoxy-*N*,2-dimethyl-5-(4-phenylpiperidin-1-yl)pent-3-enamide (45): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and (*S*)-*N*-methoxy-*N*,2-dimethylpent-4-enamide[6] (31.4 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2, 1% NH_4OH-MeOH/DCM (400 mL)→2% NH_4OH-MeOH/DCM (400 mL)→3% NH_4OH-MeOH/DCM (400 mL)→4% NH_4OH-MeOH/DCM (400 mL)→5% NH_4OH-MeOH/DCM (100 mL) eluent) afforded the product as an orange oil. Run 1: 37.8 mg, 60% yield; Run 2: 40.6 mg, 64% yield; Run 3: 40.7 mg, 64% yield. **Average 63% yield (± 2.7%).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (app t, *J* = 7.5 Hz, 2H), 7.26 (app d, *J* = 7.2 Hz, 2H), 7.23 (tt, *J* = 7.2, 1.2 Hz, 1H), 5.80 (dd, *J* = 15.5, 7.6 Hz, 1H), 5.71 (dt, *J* = 15.4, 6.5 Hz, 1H), 3.74 (s, 3H), 3.71 – 3.64 (m, 1H), 3.22 (s, 3H), 3.15 – 3.04 (m, 4H), 2.53 (tt, *J* = 10.9, 5.6 Hz, 1H), 2.10 (td, *J* = 10.5, 4.0 Hz, 2H), 1.91 – 1.81 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 175.68, 146.36, 133.92, 128.48, 127.95, 126.93, 126.20, 61.58, 61.06, 54.35, 54.24, 42.70, 38.83, 33.47, 32.35, 17.83. HRMS (ES+) m/z calc'd for $C_{19}H_{29}N_2O_2$ [M+H]+: 317.2229; found 317.2232. $[\alpha]^{22}_D$ = 12.37 (c = 0.98, $CHCl_3$).



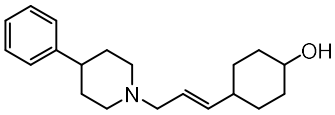
(*S*,*E*)-1-(4,8-dimethylnona-2,7-dien-1-yl)-4-phenylpiperidine (46): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and (*S*)-4,8-dimethylnona-1,7-diene[7] (30.5 mg, 0.2 mmol, 1.0 eq) were reacted according to

general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (40 mL Brockmann Grade 3 alumina, Hx (200 mL)→2% EtOAc/Hx (200 mL)→4% EtOAc/Hx (200 mL)→6% EtOAc/Hx (200 mL) eluent) afforded the product as a yellow oil. Run 1: 41.8 mg, 68% yield; Run 2: 40.4 mg, 65% yield; Run 3: 42.9 mg, 69% yield. **Average 67% yield (± 1.9%).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 (app d, *J* = 7.1 Hz, 2H), 7.19 (app t, *J* = 7.4 Hz, 1H), 5.56 – 5.45 (m, 2H), 5.11 (t, *J* = 7.1 Hz, 1H), 3.12 – 3.05 (m, 2H), 3.04 – 2.96 (m, 2H), 2.49 (tt, *J* = 10.5, 5.8 Hz, 1H), 2.16 (hept, *J* = 6.8 Hz, 1H), 2.08 – 1.90 (m, 4H), 1.87 – 1.77 (m, 4H), 1.69 (s, 3H), 1.59 (s, 3H), 1.33 (q, *J* = 7.6 Hz, 2H), 1.00 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.54, 140.50, 131.37, 128.51, 126.99, 126.20, 124.95, 124.76, 61.57, 54.33, 54.23, 42.90, 37.17, 36.34, 33.60, 26.01, 25.84, 20.69, 17.79. HRMS (ES+) m/z calc'd for $C_{22}H_{34}N$ [M+H]+: 312.2691; found 312.2682. $[\alpha]^{20}_{D}$ = 19.89 (c = 0.95, $CHCl_3$).



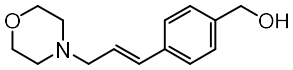
(*E*)-4-phenyl-1-(8-(triisopropylsilyl)oct-2-en-7-yn-1-yl)piperidine (47): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and triisopropyl(act-7-en-1-yn-1-yl)silane[8] (52.8 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2 deactivated with 4% triethylamine, Hx (100 mL)→0.5% Acetone/Hx (400 mL)→1% Acetone/Hx (400 mL)→1.5% Acetone/Hx (400 mL)→2% Acetone/Hx (400 mL)→2.5% Acetone/Hx (200 mL) eluent) afforded the product as a yellow oil. Run 1: 51.8 mg, 61% yield; Run 2: 52.3 mg, 62% yield; Run 3: 51.9 mg, 61% yield. **Average 62% yield (± 0.4%).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (app t, *J* = 7.3 Hz, 2H),

7.23 (app d, J = 7.2 Hz, 2H), 7.19 (tt, J = 7.3, 1.3 Hz, 1H), 5.65 – 5.55 (m, 2H), 3.10 – 3.04 (m, 2H), 3.00 (d, J = 4.7 Hz, 2H), 2.54 – 2.44 (m, 1H), 2.27 (t, J = 7.0 Hz, 2H), 2.23 – 2.16 (m, 2H), 2.03 (td, J = 11.2, 4.5 Hz, 2H), 1.89 – 1.78 (m, 4H), 1.63 (p, J = 7.1 Hz, 2H), 1.15 – 0.97 (m, 21H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.51, 133.52, 128.51, 127.44, 126.98, 126.21, 108.85, 80.51, 61.40, 54.30, 42.87, 33.58, 31.45, 28.58, 19.46, 18.77, 11.42. HRMS (ES+) m/z calc'd for $C_{28}H_{46}NSi$ [M+H]+: 424.3400; found 424.3393.

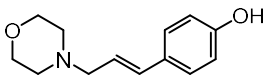


(*E*)-4-(3-(4-phenylpiperidin-1-yl)prop-1-en-1-yl)cyclohexan-1-ol (48): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and 4-allylcyclohexan-1-ol (28.0 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. The crude mixture was diluted with 25 mL of EtOAc, stirred over 5 mL of Brockmann Grade 3 alumina for 15 minutes, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (50 mL SiO_2, 0.5% NH_4OH-MeOH/DCM (200 mL)→1.5% NH_4OH-MeOH/DCM (200 mL)→2.5% NH_4OH-MeOH/DCM (200 mL)→3.5% NH_4OH-MeOH/DCM (200 mL)→4.5% NH_4OH-MeOH/DCM (200 mL)→5% NH_4OH-MeOH/DCM (200 mL)→5.5% NH_4OH-MeOH/DCM (200 mL)→6% NH_4OH-MeOH/DCM (200 mL)→6.5% NH_4OH-MeOH/DCM (200 mL) eluent) afforded the product as a beige oil. Run 1: 40.9 mg, 69% yield; Run 2: 40.3 mg, 68% yield; Run 3: 43.0 mg, 72% yield. **Average 70% yield (± 2.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (t, J = 7.6 Hz, 2H), 7.22 (app d, J = 7.4 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 5.70 – 5.48 (m, 2H), 3.99 – 3.90 (m, 0.24H), 3.54 (tt, J = 10.7, 4.3 Hz, 0.77H), 3.12 – 3.05 (m, 2H), 3.03 (d, J = 6.4 Hz, 0.42H), 3.00 (d, J = 4.9 Hz, 1.42H), 2.54 – 2.43 (m, 1H), 2.12 – 2.01 (m, 2.5H), 2.01 – 1.91 (m, 2.5H), 1.87 – 1.76 (m, 5.5H), 1.74 – 1.67 (m,

0.5H), 1.62 – 1.51 (m, 1H), 1.35 – 1.23 (m, 2H), 1.21 – 1.11 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.20, 139.73, 128.50, 126.93, 126.25, 124.08, 70.49, 66.75, 61.46, 61.37, 61.32, 54.32, 54.3, 54.10, 54.08, 42.65, 42.62, 39.63, 38.89, 35.33, 34.96, 33.36, 33.32, 33.24, 33.20, 32.17, 31.00, 30.84, 27.00, 22.88. HRMS (ES+) m/z calc'd for $C_{20}H_{30}NO$ [M+H]+: 300.2327; found 300.2321.

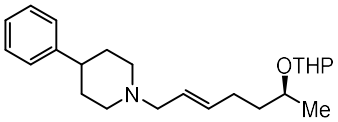


(E)-(4-(3-morpholinoprop-1-en-1-yl)phenyl)methanol (49): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and (4-allylphenyl)methanol (29.6 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 12 hours. The crude mixture was diluted with 25 mL of EtOAc, stirred over 5 mL of Brockmann Grade 3 alumina for 15 minutes, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 0→1→2→3→5% MeOH/DCM) afforded the product as a yellow oil. Run 1: 42.4 mg, 91% yield; Run 2: 43.5 mg, 93% yield; Run 3: 41.5 mg, 89% yield. **Average 91% yield (±2.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.66 (s, 2H), 3.72 (app t, *J* = 4.7 Hz, 4H), 3.13 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.48 (app br s, 4H), 2.33 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.60, 136.24, 133.24, 127.31, 126.60, 126.00, 67.01, 64.99, 61.57, 53.76. HRMS (ESI) m/z calc'd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494; found 234.1491.



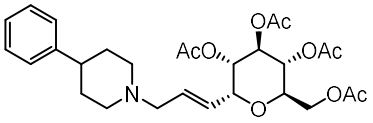
(E)-4-(3-morpholinoprop-1-en-1-yl)phenol (50): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 4-allylphenol (26.8 mg , 0.2

mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. The crude mixture was filtered through a plug of celite and Brockmann Grade 3 alumina. Purification *via* flash column chromatography (SiO_2, 0→1→3→5→20% MeOH/DCM) afforded the product as a yellow oil. 1: 27.6 mg, 63% yield; Run 2: 29.3 mg, 67% yield; Run 3: 27.9 mg, 64% yield. **Average 65% yield (±2.1%)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.05 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.77 (app t, *J* = 4.7 Hz, 4H), 3.17 (d, *J* = 7.2 Hz, 2H), 2.57 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.01, 134.01, 129.20, 127.93, 122.41, 115.92, 66.74, 61.55, 53.57. HRMS (ESI) m/z calc'd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338; found 220.1343.



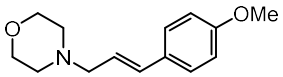
4-phenyl-1-((6*S*,*E*)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hept-2-en-1-yl)piperidine (51): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and 2-(((*S*)-hept-6-en-2-yl)oxy)tetrahydro-2*H*-pyran (39.6 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2 deactivated with 4% triethylamine, Hx (200 mL)→2% Acetone/Hx (200 mL)→4% Acetone/Hx (200 mL)→6% Acetone/Hx (200 mL)→8% Acetone/Hx (200 mL)→10% Acetone/Hx (200 mL) eluent) afforded the product as a yellow oil. Run 1: 44.1 mg, 62% yield; Run 2: 47.5 mg, 66% yield; Run 3: 47.6 mg, 67% yield. **Average 65% yield (± 2.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (app t, *J* = 7.5 Hz, 2H), 7.22 (app d, *J* = 7.2 Hz, 2H), 7.18 (app t, *J* = 7.2 Hz, 1H), 5.68 – 5.51 (m, 2H), 4.72 – 4.68 (m, 0.5H), 4.62 (dd, *J* = 5.0, 2.8 Hz,

0.5H), 3.96 – 3.84 (m, 1H), 3.80 (app sext, *J* = 6.3 Hz, 0.5H), 3.73 (sext, *J* = 6.3 Hz, 0.5H), 3.51 – 3.44 (m, 1H), 3.11 – 3.03 (m, 2H), 2.99 (dd, *J* = 6.5, 3.0 Hz, 2H), 2.53 – 2.44 (m, 1H), 2.27 – 1.97 (m, 4H), 1.87 – 1.77 (m, 5H), 1.75 – 1.43 (m, 7H), 1.23 (d, *J* = 6.3 Hz, 1.5H), 1.11 (d, *J* = 6.1 Hz, 1.5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.41, 134.58, 134.32, 128.49, 126.96, 126.68, 126.40, 126.21, 98.99, 95.70, 73.64, 70.66, 62.96, 62.61, 61.36, 61.34, 54.24, 54.18, 42.79, 37.16, 36.21, 33.45, 31.32, 31.30, 28.88, 28.49, 25.65, 25.60, 21.74, 20.20, 19.87, 19.20. HRMS (ES+) m/z calc'd for $C_{23}H_{36}NO_2$ [M+H]+: 358.2746; found 358.2735.

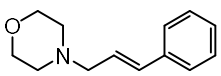


(2*R*,3*R*,4*R*,5*S*,6*R*)-2-(acetoxymethyl)-6-((*E*)-3-(4-phenylpiperidin-1-yl)prop-1-en-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (52): 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and (*2R,3R,4R,5S,6R*)-2-(acetoxymethyl)-6-allyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate[11] (74.5 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (50 mL SiO_2, 0.5% NH_4OH-MeOH/DCM (400 mL)→1% NH_4OH-MeOH/DCM (400 mL)→1.5% NH_4OH-MeOH/DCM (400 mL)→2% NH_4OH-MeOH/DCM (400 mL)→2.5% NH_4OH-MeOH/DCM (400 mL) eluent) afforded the product as a beige solid. Run 1: 91.8 mg, 86% yield; Run 2: 90.6 mg, 85% yield; Run 3: 91.2 mg, 86% yield. **Average 86% yield (± 0.6%).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 (app t, *J* = 7.6 Hz, 2H), 7.20 (app d, *J* = 7.1 Hz, 2H), 7.16 (app t, *J* = 7.2 Hz, 1H), 5.98 (dt, *J* = 15.7, 6.5 Hz, 1H), 5.86 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.31 (app t, *J* = 9.7 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.74 (app t, *J* = 6.3 Hz, 1H), 4.20 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.05 (dd, *J* = 12.3, 2.4 Hz, 1H), 3.94 (ddd, *J* = 9.9, 4.8, 2.4 Hz, 1H), 3.14 (dd, *J* = 13.6, 6.1 Hz, 1H), 3.06 (dd, *J* = 13.8, 7.1 Hz, 1H), 3.03 – 2.98 (m, 2H), 2.48 (tt, *J* = 11.5, 4.4

Hz, 1H), 2.13 – 2.02 (m, 2H), 2.06 (s, 3H), 2.00 (2 x s, 6H), 1.99 (s, 3H), 1.87 – 1.72 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.65, 170.24, 169.55, 169.50, 146.14, 135.65, 128.45, 126.84, 126.21, 124.79, 72.91, 70.71, 70.42, 69.37, 69.07, 62.35, 60.76, 54.46, 54.13, 42.55, 33.45, 33.42, 20.77, 20.73, 20.71, 20.65. HRMS (ES+) m/z calc'd for $C_{28}H_{38}NO_9$ [M+H]+: 532.2547; found 532.2540. $[\alpha]^{22}_D$ = 89.89 (c = 0.92, $CHCl_3$).

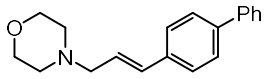


(E)-4-(3-(4-methoxyphenyl)allyl)morpholine (53) morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 1-allyl-4-methoxybenzene (29.6 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→10→50% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 42.6 mg, 91% yield; Run 2: 44.0 mg, 94% yield; Run 3: 43.5 mg, 93% yield. **Average 93% yield (±1.4%)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.11 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.74 (app t, *J* = 4.7 Hz, 4H), 3.13 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.51 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.34, 133.06, 129.75, 127.63, 123.82, 114.14, 67.13, 61.72, 55.45, 53.81. HRMS (ESI) m/z calc'd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494; found 234.1496.

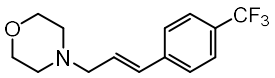


4-cinnamylmorpholine (54): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and allylbenzene (23.6 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred

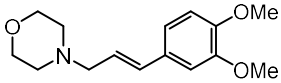
24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→3→5→10% EtOAc/Hx) afforded the product as a yellow solid. Run 1: 30.5 mg, 75% yield; Run 2: 30.2 mg, 74% yield; Run 3: 30.8 mg, 76% yield. **Average 75% yield (±0.7%)**. ^{1}H NMR (499 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.74 (app t, *J* = 4.7 Hz, 4H), 3.16 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.51 (app br s, *J* = 4.6 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.91, 133.56, 128.70, 127.71, 126.45, 126.11, 67.09, 61.58, 53.80. HRMS (ESI) m/z calc'd for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388; found 204.1383.



(E)-4-(3-([1,1'-biphenyl]-4-yl)allyl)morpholine (55): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 4-allyl-1,1'-biphenyl (38.9 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→10% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 50.2 mg, 90% yield; Run 2: 48.7 mg, 87% yield; Run 3: 50.0 mg, 89% yield. **Average 89% yield (±1.3)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.52 (m, 4H), 7.50 – 7.40 (m, 4H), 7.37 – 7.31 (m, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.31 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.75 (app t, *J* = 4.7 Hz, 4H), 3.18 (dd, *J* = 6.8, 1.4 Hz, 2H), 2.52 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.81, 140.49, 135.98, 133.06, 128.93, 127.46, 127.43, 127.07, 126.89, 126.39, 67.17, 61.68, 53.89. HRMS (ESI) m/z calc'd for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1701; found 280.1703.

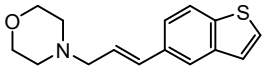


(E)-4-(3-(4-(trifluoromethyl)phenyl)allyl)morpholine (56): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 1-allyl-4-(trifluoromethyl)benzene (37.2 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* by flash column chromatography (Brockmann Grade 3 alumina, 0→3→5→20% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 44.5 mg, 82% yield; Run 2: 45.0 mg, 83% yield; Run 3: 44.4 mg, 82% yield. **Average 82% yield (±0.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.35 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.74 (app t, *J* = 4.7 Hz, 4H), 3.17 (d, *J* = 6.7 Hz, 1.0 Hz, 2H), 2.50 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.37, 132.03, 129.48 (q, J_{CF} = 32.3 Hz), 129.14, 126.57, 125.66 (q, J_{CF} = 3.8 Hz), 124.29 (q, J_{CF} = 272.3 Hz), 67.06, 61.35, 53.85. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.41. HRMS (ESI) m/z calc'd for $C_{14}H_{17}NOF_3$ $[M+H]^+$: 272.1262; found 272.1261.

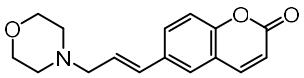


(E)-4-(3-(3,4-dimethoxyphenyl)allyl)morpholine (57): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 4-allyl-1,2-dimethoxybenzene (35.6 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. The crude mixture was diluted with 10 mL of EtOAc and stirred with 5 mL of Brockmann Grade 3 alumina for 15 minutes. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→10→20% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 44.4 mg,

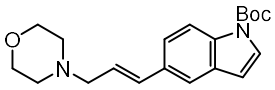
84% yield; Run 2: 43.2 mg, 82% yield; Run 3: 43.9 mg, 83% yield. **Average 83% yield (±1.0%)**. ^{1}H NMR (499 MHz, Chloroform-*d*) δ 6.95 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.46 (dt, *J* = 15.9, 1H), 6.12 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.74 (app t, *J* = 4.7 Hz, 4H), 3.14 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.51 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.18, 148.96, 133.28, 130.02, 124.10, 119.68, 111.22, 108.70, 67.12, 61.64, 56.07, 55.93, 53.82. HRMS (ESI) m/z calc'd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1600; found 264.1598.



(E)-4-(3-(benzo[b]thiophen-5-yl)allyl)morpholine (58): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 5-allylbenzo[b]thiophene (34.9 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→10→30% EtOAc/Hx) afforded the product as a yellow oil. 1: 38.4 mg, 74% yield; Run 2: 40.7 mg, 78% yield; Run 3: 38.9 mg, 75% yield. **Average 76% yield (±2.1%)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.30 (d, *J* = 5.5 Hz, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.31 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.75 (app t, *J* = 4.7 Hz, 4H), 3.19 (dd, *J* = 6.8, 1.4 Hz, 2H), 2.53 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.13, 139.06, 133.67, 133.38, 127.08, 125.72, 124.03, 122.65, 122.55, 121.82, 67.12, 61.67, 53.83. HRMS (ESI) m/z calc'd for $C_{15}H_{18}NOS$ $[M+H]^+$: 260.1109; found 260.1101.

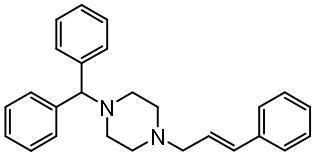


(E)-6-(3-morpholinoprop-1-en-1-yl)-2H-chromen-2-one (59): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and 6-allyl-2H-chromen-2-one (37.2 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→10→20→30→40→60→70% EtOAc/Hx) afforded the product as a yellow oil. 1: 29.8 mg, 55% yield; Run 2: 30.9 mg, 57% yield; Run 3: 29.3 mg, 54% yield. **Average 55% yield (±1.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 9.6 Hz, 1H), 7.55 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.74 (app t, *J* = 4.7 Hz, 4H), 3.18 (dd, *J* = 6.8, 1.5 Hz, 2H), 2.52 (app br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.70, 153.53, 143.39, 133.65, 131.48, 129.72, 127.54, 125.47, 119.01, 117.28, 117.18, 67.11, 61.38, 53.87. HRMS (ESI) m/z calc'd for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1287; found 272.1285.

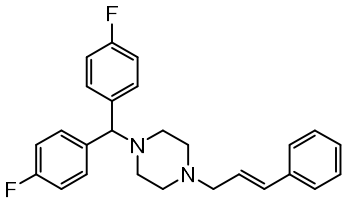


tert-butyl (E)-5-(3-morpholinoprop-1-en-1-yl)-1H-indole-1-carboxylate (60): morpholine-borontrifluoride (36.2 mg, 0.2 mmol, 1 eq) and tert-butyl 5-allyl-1H-indole-1-carboxylate (51.5 mg , 0.2 mmol, 1 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.25 M dibutylphosphate solution in dioxane (0.25 eq) as a solvent for and stirred 24 hours. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→7→10→30% EtOAc/Hx) afforded the product as a yellow oil. 1: 55.1 mg, 80% yield; Run 2: 51.6 mg, 75% yield; Run 3: 52.5 mg, 76% yield. **Average 77% yield (±2.7%)**.

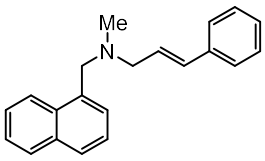
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 3.7 Hz, 1H), 7.53 (app s, 1H), 7.37 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 6.25 (dt, *J* = 15.6, 6.8 Hz, 1H), 3.75 (app t, *J* = 4.6 Hz, 4H), 3.18 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.53 (app br s, 4H), 1.67 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.76, 134.84, 133.94, 131.72, 130.98, 126.54, 124.71, 122.79, 118.99, 115.30, 107.47, 83.88, 67.13, 61.73, 53.82, 28.34. HRMS (ESI) m/z calc'd for $C_{20}H_{27}N_2O_3$ $[M+H]^+$: 343.2022; found 343.2030.



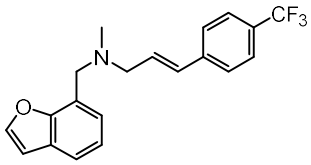
1-benzhydryl-4-cinnamylpiperazine (61): 1-benzhydrylpiperazine-borontrifluoride and allylbenzene (23.6 mg, 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.25 M solution of dibutylphosphate in toluene as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→15% EtOAc/Hx eluent) afforded the product as a white solid. Run 1: 69.5 mg, 94% yield; Run 2: 70.6 mg, 96% yield; Run 3: 71.4 mg, 97% yield. **Average 96% yield (±1.3%)**. Spectral data were in accordance to literature values.



1-(bis(4-fluorophenyl)methyl)-4-cinnamylpiperazine (62): 1-(4-methoxyphenyl)-N-methylmethanamine-borontrifluoride and allylbenzene (23.6 mg, 0.2 mmol, 1 eq) were reacted according to general procedure **B**. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→2→5→7.5→10% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 69.3 mg, 86% yield; Run 2: 69.6 mg, 86% yield; Run 3: 71.2 mg, 88% yield. **Average 87% yield (±1.3%)**. Spectral data were in accordance to literature values.

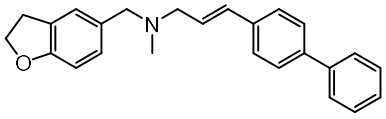


(E)-N-methyl-N-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine (63): N-methyl-1-(naphthalen-1-yl)methanamine-borontrifluoride and allylbenzene (23.6 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in MTBE as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5→30% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 52.3 mg, 91% yield; Run 2: 50.6 mg, 88% yield; Run 3: 51.7 mg, 90% yield. **Average 90% yield (±1.5%)**. Spectral data were in accordance to literature values[2]

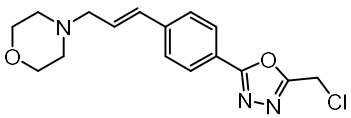


***N*-methyl-*N*-[(2*E*)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl-7-benzofuranmethanamine (64):** 1-(benzofuran-7-yl)-N-methylmethanamine-borontrifluoride (45.8 mg, 0.2 mmol, 1.0 eq) and 1-allyl-4-(trifluoromethyl)benzene (37.2 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.5M solution of dibutyl phosphate in MTBE (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0 → 20% EtOAc/Hx eluent) afforded the product as a yellow oil. Run 1: 57.6 mg, 83% yield; Run 2: 55.8 mg, 81% yield; Run 3: 55.3 mg, 80% yield. **Average 81% yield (±1.2%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.53 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.5, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.45 (dt, *J* = 15.9, 6.5 Hz, 1H), 3.90 (s, 2H), 3.29 (d, *J* = 6.3 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.01, 144.98, 140.75, 131.26, 130.73, 129.28 (q, *J* = 32.4 Hz), 127.55, 126.56, 125.63 (q, *J* = 3.8 Hz), 125.54, 124.37 (q, *J* = 271.8 Hz),

122.88, 122.38, 120.35, 106.84, 59.95, 55.92, 42.73. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.45. HRMS (ESI) m/z calc'd for $C_{20}H_{18}F_3NO$ $[M+H]^+$: 346.1340; found 346.1429.

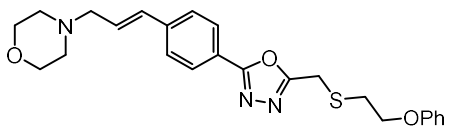


(E)-3-([1,1'-biphenyl]-4-yl)-N-((2,3-dihydrobenzofuran-5-yl)methyl)-N-methylprop-2-en-1-amine (65): 1-(2,3-dihydrobenzofuran-5-yl)-N-methylmethanamine-borontrifluoride and 4-allyl-1,1'-biphenyl (38.9 mg , 0.2 mmol, 1 eq) were reacted according to general procedure using 0.2 mL of a 0.5 M solution of dibutylphosphate in MTBE as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→2→5→10% EtOAc/Hx) afforded the product as a cloudy oil. Run 1: 47.5 mg, 67% yield; Run 2: 49.7 mg, 70% yield; Run 3: 49.1 mg, 69% yield. **Average 69% yield (±1.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.49 – 7.40 (m, 4H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.57 (t, *J* = 8.7 Hz, 2H), 3.49 (s, 2H), 3.26 – 3.16 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.33, 140.83, 140.23, 136.28, 132.18, 130.95, 129.05, 128.88, 127.95, 127.36, 127.34, 127.16, 127.02, 126.82, 125.93, 108.81, 71.37, 61.72, 59.91, 42.21, 29.83. HRMS (ESI) m/z calc'd for $C_{25}H_{26}NO$ $[M+H]^+$: 356.2014; found 356.2016.



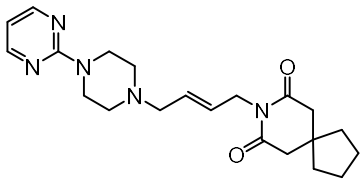
(E)-4-(3-(4-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)phenyl)allyl)morpholine (66): Morpholine-borontrifluoride (31.0 mg, 0.2 mmol, 1.0 eq) and 2-(4-allylphenyl)-5-(chloromethyl)-1,3,4-oxadiazol (46.9 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.25M solution of dibutyl phosphate in toluene (0.25 eq) as a solvent and stirred for 48 h. Purification *via* flash

column chromatography (Brockmann Grade 3 alumina, 0 → 20% → 30% → 80% EtOAc/Hx) eluent followed by a second column chromatography (SiO_2, 0% → 5% → 8% MeOH/EtOAc) afforded (E)-4-(3-(4-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)phenyl)allyl)morpholine as an off-white solid. Run 1: 49.8 mg, 78% yield; Run 2: 51.8 mg, 81% yield; Run 3: 52.4 mg, 82% yield. **Average 80% yield (±1.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.41 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.77 (s, 2H), 3.75 (app t, *J* = 4.7 Hz, 4H), 3.19 (dd, *J* = 6.6, 1.4 Hz, 2H), 2.52 (app br s, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.02, 162.16, 140.81, 132.19, 129.44, 127.56, 127.08, 122.21, 67.11, 61.43, 53.90, 33.17. HRMS (ESI -TOF ES+) m/z calc'd for $C_{16}H_{18}ClN_3O_2$ $[M+H]^+$: 320.1121; found 320.1156.

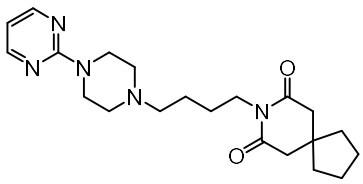


(E)-4-(3-(4-(5-(((2-phenoxyethyl)thio)methyl)-1,3,4-oxadiazol-2-yl)phenyl)allyl)morpholine (67): To an oven-dried flask and stir bar was added 2-phenoxyethane-1-thiol (50 μL, 0.34 mmol, 1.1 eq) and dry THF (3.1 mL, 0.1 M) and then 95% NaH (11.4 mg, 0.48 mmol, 1.5 eq). The suspension was stirred for 30 minutes at room temperature. To the flask was added (E)-4-(3-(4-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)phenyl)allyl)morpholine (100 mg, 0.31 mmol, 1.0 eq). The flask was topped with an oven-dried reflux condenser, heated to 60 ºC, and stirred for 8 hours under argon. The mixture was cooled to room temperature, quenched with H_2O (15 mL), and diluted with EtOAc (15 mL). The layers were separated, and the aqueous layer was washed with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, and then filtered. Volatiles were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 0 → 0.5% → 1% → 1.5% MeOH/$CHCl_3$ eluent) afforded (E)-4-(3-(4-(5-(((2-

phenoxyethyl)thio)methyl)-1,3,4-oxadiazol-2-yl)phenyl)allyl)morpholine as green-yellow semi-solid (106 mg, 0.24 mmol, 78% yield). Spectral data were in accordance to literature values.

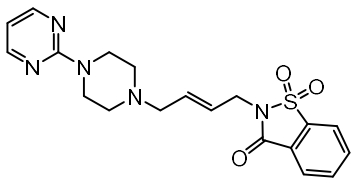


(E)-8-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione: 2-(piperazin-1-yl)pyrimidine-borontrifluoride (46.4 mg, 0.2 mmol, 1 eq) and 8-(but-3-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (44.3 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0 → 20 → 25 → 40 → 50% EtOAc/Hx) afforded the product as a yellow oil. Run 1: 63.4 mg, 83% yield; Run 2: 61.3 mg, 80% yield; Run 3: 61.3 mg, 80% yield. **Average 81% yield (±1.6%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 4.7 Hz, 2H), 6.49 (t, *J* = 4.8 Hz, 1H), 5.74 (dt, *J* = 14.8, 6.5 Hz, 1H), 5.64 (dt, *J* = 15.4, 5.9 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (app t, *J* = 5.1 Hz, 4H), 3.01 (d, *J* = 6.5 Hz, 2H), 2.62 (s, 4H), 2.47 (app t, *J* = 5.1 Hz, 4H), 1.78 – 1.70 (m, 4H), 1.58 – 1.49 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.98, 161.81, 157.82, 130.15, 127.98, 109.94, 60.49, 53.01, 44.98, 43.77, 40.72, 39.72, 37.74, 24.34. HRMS (ESI) m/z calc'd for $C_{21}H_{30}N_5O_2$ $[M+H]^+$: 384.2400; found 384.2384.

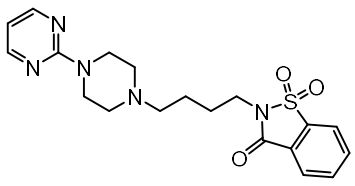


buspirone (68): An oven dried RBF was charged with (E)-8-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (61.3 mg, 0.16 mmol, 1 eq), Pd/C (30 wt%, 6 mg, 0.017 mmol, 0.1 eq), and EtOAc (1.25 mL, 0.13M). The vessel was quickly placed under vacuum and backfilled with N_2 two times, and H_2 one time. The mixture was stirred at room

temperature for 23.5 hr. Afterwards, the crude mixture was passed through a plug of celite and flushed with EtOAc. Purification *via* flash column chromatography (SiO_2, 0% → 10% MeOH/EtOAc) afforded buspirone (34.3 mg, 0.089 mmol, 56% yield). Spectra were in accordance to literature values.

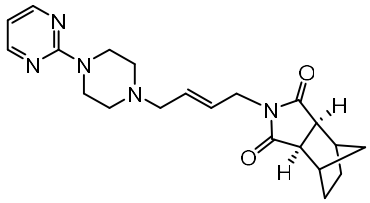


(E)-2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide: 2-(piperazin-1-yl)pyrimidine-borontrifluoride (46.4 mg, 0.2 mmol, 1 eq) and 2-(but-3-en-1-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (47.5 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in toluene (0.5 eq) as a solvent and stirred for 72 h.. Purification *via* flash column chromatography (SiO_2, 80% EtOAc/Hx →0%→2%→5% MeOH/EtOAc as an eluent) afforded the product as a beige solid. Run 1: 55.2 mg, 69% yield; Run 2: 54.5 mg, 68% yield; Run 3: 51.4 mg, 64% yield. **Average 67% yield (±2.6%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 4.8 Hz, 2H), 8.06 (d, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.86 (t, *J* = 7.3 Hz, 1H), 7.83 (t, *J* = 7.3 Hz, 1H), 6.46 (t, *J* = 4.8 Hz, 1H), 5.96 (dt, *J* = 15.1, 6.6 Hz, 1H), 5.80 (dt, *J* = 15.3, 6.2 Hz, 1H), 4.39 (d, *J* = 6.2 Hz, 2H), 3.83 (app t, *J* = 5.1 Hz, 4H), 3.06 (d, *J* = 6.5 Hz, 2H), 2.51 (app t, *J* = 5.1 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.79, 158.66, 157.80, 137.96, 134.91, 134.44, 132.46, 127.48, 126.11, 125.34, 121.07, 109.95, 60.11, 52.98, 43.70, 40.53. HRMS (ESI) m/z calc'd for $C_{19}H_{22}N_5O_3S$ $[M+H]^+$: 400.1443; found 400.1443.

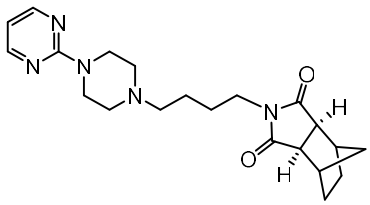


ipsapirone (69): An oven dried RBF was charged with (*E*)-2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)benzo[*d*]isothiazol-

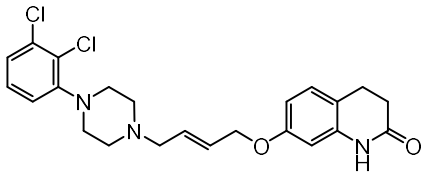
3(2*H*)-one 1,1-dioxide (46.8 mg, 0.117 mmol, 1 eq), Pd/C (30 wt%, 1.4 mg, 0.004 mmol, 0.03 eq), and EtOH (10 mL, 0.01 M). The vessel was quickly placed under vacuum and backfilled with N_2 two times, and H_2 one time. The mixture was stirred at room temperature for 23.5 hr. Afterwards, the crude mixture was passed through a plug of celite and flushed with EtOAc. Purification *via* flash column chromatography (SiO_2, 0% → 1% → 2% MeOH/EtOAc) afforded ipsapirone as a white solid (28 mg, 0.070 mmol, 60% yield). Spectral data in accordance with literature values.



(3aR,7aS)-2-((E)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione: 2-(piperazin-1-yl)pyrimidine-borontrifluoride (46.4 mg, 0.2 mmol, 1 eq) and (3aR,4S,7R,7aS)-2-(but-3-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (43.9 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in toluene (0.5 eq) as a solvent and stirred for 48 h.. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 20→22.5→25→30→35% EtOAc/Hx) afforded the product as a cloudy white oil. Run 1: 54.2 mg, 71% yield; Run 2: 54.9 mg, 72% yield; Run 3: 51.8 mg, 68% yield. **Average 70% yield (±2.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 4.7 Hz, 2H), 6.47 (t, *J* = 4.7 Hz, 1H), 5.77 (dt, *J* = 15.7, 6.6 Hz, 1H), 5.60 (dt, *J* = 15.5, 6.2 Hz, 1H), 4.06 (d, *J* = 6.2 Hz, 2H), 3.81 (app t, *J* = 5.0 Hz, 4H), 2.99 (d, *J* = 6.5 Hz, 2H), 2.70 (s, 2H), 2.60 (s, 2H), 2.45 (app t, *J* = 5.1 Hz, 4H), 1.66 (app d, *J* = 8.1 Hz, 2H), 1.34 (app d, *J* = 6.4 Hz, 2H), 1.22 (d, *J* = 11.0 Hz, 1H), 1.08 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.54, 161.76, 157.79, 131.31, 126.49, 109.93, 60.27, 53.00, 48.76, 43.72, 39.94, 39.91, 33.22, 28.15. HRMS (ESI) m/z calc'd for $C_{21}H_{28}N_5O_2$ $[M+H]^+$: 382.2243; found 382.2238.

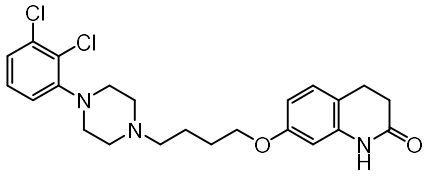


tandospirone (70): An oven dried RBF was charged with (3aR,7aS)-2-((E)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)but-2-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (48.1 mg, 0.126 mmol, 1 eq), Pd/C (30 wt%, 8 mg, 0.02 mmol, 0.18 eq), and EtOH (1.5 mL, 0.08 M). The vessel was quickly placed under vacuum and backfilled with N_2 two times, and H_2 one time. The mixture was stirred at room temperature for 36 hr. Afterwards, the crude mixture was passed through a plug of celite and flushed with EtOAc. Purificaltion *via* flash column chromatography (SiO2, 0% → 1% → 2% → 4% → 8% MeOH/EtOAc) afforded tandospirone (30.7 mg, 0.08 mmol, 64% yield) as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 4.7 Hz, 2H), 6.46 (t, *J* = 4.7 Hz, 1H), 3.81 (app t, *J* = 5.0 Hz, 4H), 3.48 (t, *J* = 7.2 Hz, 2H), 2.69 (br s, 2H), 2.58 (s, 2H), 2.48 (app t, *J* = 5.0 Hz, 4H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.66 (app d, *J* = 8.6 Hz, 2H), 1.59 (p, *J* = 7.4 Hz, 2H), 1.51 (p, *J* = 7.2 Hz, 2H), 1.33 (app d, *J* = 8.1 Hz, 2H), 1.21 (d, *J* = 11.0 Hz, 1H), 1.09 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.10, 161.75, 157.82, 109.93, 58.20, 53.19, 48.74, 43.72, 39.87, 38.64, 33.26, 28.17, 25.97, 24.27. HRMS (ESI) m/z calc'd for $C_{21}H_{30}N_5O_2$ $[M+H]^+$: 384.2400; found 384.2389



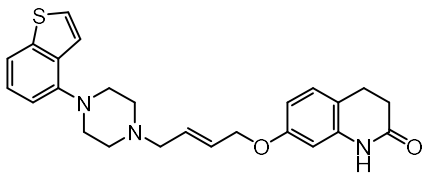
(*E*)-7-((4-(4-(2,3-dichlorophenyl)piperazin-1-yl)but-2-en-1-yl)oxy)-3,4-dihydroquinolin-2(1H)-one: 1-(2,3-dichlorophenyl)piperazine-borontrifluoride (59.8 mg, 0.2 mmol, 1.0 eq) and 27-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1H)-one (43.5 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.5M solution of dibutyl phosphate in benzene (0.50 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (SiO_2 deactivated with 2% triethylamine/DCM, 20% → 25% → 30% → 35% →

40% Acetone/Hx eluent) followed by a second column chromatography (SiO_2, 0% → 0.5% → 1% → 1.5% → 2.0% → 2.5% → 3.0% NH_4OH-MeOH/DCM) afforded (E)-7-((4-(4-(2,3-dichlorophenyl)piperazin-1-yl)but-2-en-1-yl)oxy)-3,4-dihydroquinolin-2(1H)-one as an off-white solid. Run 1: 49.3 mg, 55% yield; Run 2: 51.2 mg, 57% yield; Run 3: 53.8 mg, 60% yield. **Average 57% yield (±2.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.90 – 8.71 (m, 1H), 7.17 – 7.09 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.95 (dd, *J* = 7.1, 2.6 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.41 – 6.37 (m, 1H), 5.97 – 5.82 (m, 2H), 4.50 (d, *J* = 4.8 Hz, 2H), 3.12 (d, *J* = 5.9 Hz, 2H), 3.08 – 3.05 (m, 4H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.68 – 2.63 (m, 4H), 2.61 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.18, 158.26, 151.34, 138.35, 134.13, 130.82, 128.72, 128.67, 127.61, 127.57, 124.70, 118.73, 116.08, 109.09, 102.62, 68.36, 60.37, 53.34, 51.38, 31.16, 24.69. HRMS (ESI – TOF ES+) m/z calc'd for $C_{23}H_{25}Cl_2N_3O_2$ $[M+H]^+$: 446.1357; found 446.1398.



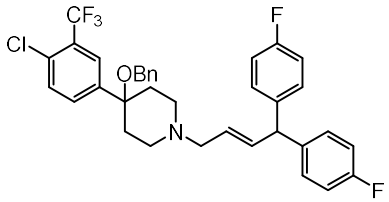
aripiprazole (71): To a N_2-flushed 1 dram vial was added (*E*)-7-((4-(4-(2,3-dichlorophenyl)piperazin-1-yl)but-2-en-1-yl)oxy)-3,4-dihydroquinolin-2(1H)-one (44.7 mg, 0.1 mmol, 1 eq), 2:1 MeOH:EtOAc (1.5 mL, 0.07M), and 3 M HCl in MeOH (40 µL, 0.12 mmol, 1.2 eq). The mixture was stirred for 10 minutes at room temperature. To the mixture was added 30 wt% Pd/C (3 mg, 2 wt% Pd w.r.t to substrate). The solution was placed in a pressure reactor and purged with H_2 (3x, 60 PSI). The mixture was then placed under H_2 (60 PSI) and stirred at room temperature for 30 minutes under H_2. The resulting solution was filtered through celite, and the plug was washed with MeOH. Solvent was removed under reduced pressure, and the resulting mixture was diluted in DCM (20 mL) and 1 M NaOH (10 mL). Layers were separated, and the aqueous layer was washed with DCM (3 x 20 mL). The combined organic layers were dried with Na_2SO_4,

filtered, and solvents were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 3% MeOH/$CHCl_3$) afforded aripiprazole as a white solid (25.2 mg, 0.056 mmol, 56% yield). Spectral data were in accordance to literature values.

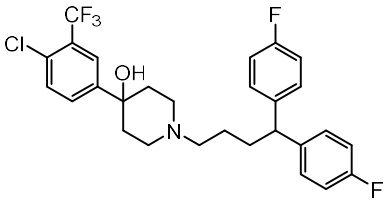


(*E*)-7-((4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)but-2-en-1-yl)oxy)-3,4-dihydroquinolin-2(1H)-one (72): 1-(benzo[*b*]thiophen-4-yl)piperazine-borontrifluoride (57.2 mg, 0.2 mmol, 1.0 eq) and 7-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1H)-one (43.5 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.5M solution of dibutyl phosphate in benzene (0.50 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (SiO_2, 0% → 1% → 2% → 3% NH_4OH-MeOH/DCM) followed by a second column chromatography (SiO_2 deactivated with 2% triethylamine/DCM, 25% → 35% → 45% → 50% Acetone/Hx) afforded (*E*)-7-((4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)but-2-en-1-yl)oxy)-3,4-dihydroquinolin-2(1H)-one as an off-white solid with 4–7% of an inseparable olefin impurity. Run 1: 46.0 mg, 53% yield; Run 2: 45.9 mg, 53% yield; Run 3: 46.0 mg, 53% yield. **Average 53% yield (±0.1%)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 – 8.10 (m, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 5.6 Hz, 1H), 7.38 (d, *J* = 5.5 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.39 – 6.33 (m, 1H), 5.96 (dt, *J* = 15.6, 6.2 Hz, 1H), 5.90 (dt, *J* = 15.5, 5.0 Hz, 1H), 4.52 (d, *J* = 5.1 Hz, 2H), 3.27 – 3.17 (m, 4H), 3.16 (d, *J* = 6.0 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.74 – 2.70 (m, 4H), 2.62 (t, *J* = 7.9 Hz, 2H). *Tautomeric ^{1}H signals observed at δ 8.27 – 8.10, 6.39 – 6.33, and 2.62*. ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.85 (171.80), 158.30, 148.53, 141.25, 138.30, 134.21, 131.02, 128.81, 128.60, 125.15, 125.11, 121.98, 117.18, 116.16, 112.34, 109.04, 102.59, 68.42, 60.48, 53.66, 52.21, 31.19,

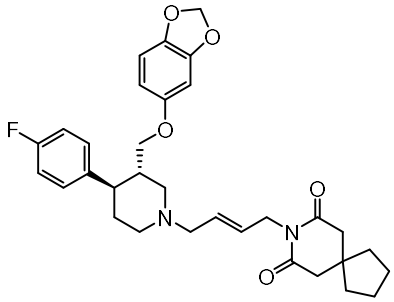
24.73. *Tautomeric ^{13}C signal observed at δ 171.80*. HRMS (ESI – TOF ES+) m/z calc'd for $C_{25}H_{27}N_3O_2S$ $[M+H]^+$: 434.1858; found 434.1889.



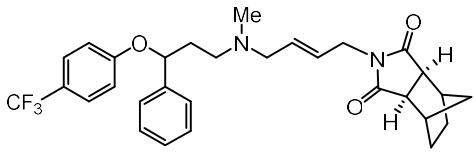
(*E*)-4-(benzyloxy)-1-(4,4-bis(4-fluorophenyl)but-2-en-1-yl)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine : 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine (87.5 mg, 0.2 mmol, 1 eq) and 4,4'-(but-3-ene-1,1-diyl)bis(fluorobenzene) (48.9 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 0→5%→6%→7% EtOAc/Hx as an eluent) afforded (*E*)-4-(benzyloxy)-1-(4,4-bis(4-fluorophenyl)but-2-en-1-yl)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine as a yellow oil. Run 1: 75.3 mg, 62% yield; Run 2: 75.3 mg mg, 62% yield; Run 3: 71.9 mg, 59% yield. **Average 61% yield (±1.6%)**. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.58 (app d, *J* = 8.5, 2.1 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 3H), 7.11 (dd, *J* = 8.4, 5.4 Hz, 4H), 6.98 (app t, *J* = 8.6 Hz, 4H), 6.06 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.49 (dt, *J* = 14.4, 6.7 Hz, 1H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.11 (s, 2H), 3.13 (d, *J* = 6.6 Hz, 2H), 2.81 (app d, *J* = 11.5 Hz, 2H), 2.50 (t, *J* = 11.8 Hz, 2H), 2.14 (app d, *J* = 12.9 Hz, 2H), 2.10 – 2.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.64 (d, *J* = 245.1 Hz), 144.61, 139.17 (d, *J* = 3.3 Hz), 138.37, 136.16, 131.77, 131.31, 130.60, 129.99 (d, *J* = 7.8 Hz), 128.58, 128.53 (q, *J* = 31.2 Hz), 127.70, 127.47, 125.37 (q, *J* = 5.5 Hz), 124.11, 123.03 (q, *J* = 273.4, 273.3, 272.4 Hz), 115.44 (d, *J* = 21.2 Hz), 75.55, 64.06, 60.82, 52.40, 49.18, 35.28. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.39, -116.46 (app tt, *J* = 9.1, 5.3 Hz). HRMS (ESI) m/z calc'd for $C_{35}H_{32}NOF_5Cl$ $[M+H]^+$: 612.2093; found 612.2084.



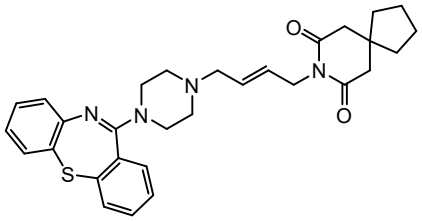
penfluridol (73): An oven dried RBF was charged with (*E*)-4-(benzyloxy)-1-(4,4-bis(4-fluorophenyl)but-2-en-1-yl)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine (59.1 mg, 0.097 mmol, 1 eq), and a fresh solution of methanolic HCl (0.5 M, 3 mL). Pd/C (30 wt%, 8.7 mg, 0.024 mmol, 0.25 eq) was added and the vessel was quickly placed under vacuum and backfilled with N_2 two times, and H_2 two times. The mixture was stirred at 50 °C for 1.5 hours. Afterwards, the crude mixture was passed through a plug of celite, flushed with MeOH, and concentrated under reduced pressure. The crude oil was dissolved in EtOAc and free based with a solution of Na_2CO_3 in water (sat.). The layers were separated, and the organic layer was extracted 2x with EtOAc. The organic layer was washed 1x with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purificaltion *via* flash column chromatography (SiO2, 0% → 1% → 2% → 3% MeOH/DCM) afforded penfluridol (33.0 mg, 0.063 mmol, 65% yield) as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 2.1 Hz, 1H), 7.59 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 5.4 Hz, 4H), 6.96 (t, *J* = 8.5 Hz, 4H), 3.88 (t, *J* = 7.8 Hz, 1H), 2.81 (d, *J* = 11.3 Hz, 2H), 2.56 – 2.34 (m, 4H), 2.15 (t, *J* = 10.9 Hz, 2H), 2.02 (q, *J* = 7.9 Hz, 2H), 1.70 (d, *J* = 13.1 Hz, 2H), 1.57 – 1.46 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.49 (d, *J* = 244.4 Hz), 147.48, 140.49 (d, *J* = 3.2 Hz), 131.50, 130.92, 129.35, 129.19 (d, *J* = 7.9 Hz), 128.27 (q, *J* = 31.2 Hz), 124.23 (q, *J* = 5.4 Hz), 123.05 (q, *J* = 273.4 Hz), 115.44 (d, *J* = 21.1 Hz), 71.08, 58.53, 49.84, 49.36, 38.24, 33.89, 25.31. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.33, -115.73 – -118.09 (m). HRMS (ESI) m/z calc'd for $C_{28}H_{28}NOClF_5$ $[M+H]^+$: 524.1780; found 524.1766.



8-((*E*)-4-((3*S*,4*R*)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl)but-2-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (74): (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-borontrifluoride (79.4 mg, 0.2 mmol, 1 eq) and 8-(but-3-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (44.3 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (Brockmann Grade 3 alumina, 17.5%→ 50% EtOAc/Hx) afforded the product as a brown oil. Run 1: 100.4 mg, 92% yield; Run 2: 102.6 mg, 94% yield; Run 3: 100.6 mg, 92% yield. **Average 92% yield (±1.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.18 – 7.09 (m, 2H), 6.95 (app t, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.86 (s, 2H), 5.74 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.62 (dt, *J* = 15.4, 6.0 Hz, 1H), 4.37 (d, *J* = 5.8 Hz, 2H), 3.55 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.41 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.19 (dd, *J* = 12.1, 2.3 Hz, 1H), 3.09 – 2.94 (m, 3H), 2.58 (s, 4H), 2.45 (td, *J* = 11.4, 4.8 Hz, 1H), 2.24 – 2.12 (m, 1H), 2.05 – 1.95 (m, 2H), 1.92 – 1.74 (m, 2H), 1.72 – 1.62 (m, 4H), 1.55 – 1.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.96, 161.61 (d, *J* = 244.2 Hz), 154.51, 148.23, 141.64, 139.80 (d, *J* = 2.3 Hz), 130.21, 128.94 (d, *J* = 7.7 Hz), 127.88, 115.50 (d, *J* = 21.1 Hz), 107.93, 105.66, 101.17, 98.15, 69.62, 60.64, 57.42, 53.88, 44.96, 44.07, 42.20, 40.72, 39.70, 37.70, 34.33, 24.30. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -116.52. HRMS (ESI) m/z calc'd for $C_{32}H_{38}N_2O_5F$ $[M+H]^+$: 549.2765; found 549.2748. $[\alpha]^{20}_D$ = -46.59 (c = 0.98, $CHCl_3$).

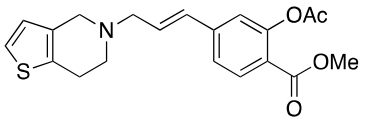


(3a*R*,4*S*,7*R*,7a*S*)-2-((*E*)-4-(methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (75): *N*-methyl-3-phenoxy-3-phenylpropan-1-amine-borontrifluoride (75.5 mg, 0.2 mmol, 1.0 eq) and (3a*R*,4*S*,7*R*,7a*S*)-2-(but-3-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (43.9 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.5M solution of dibutyl phosphate in dioxane (0.50 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (SiO_2, 0% → 0.5% → 1% → 1.5% → 1.75% → 2.0% → 2.5% NH_4OH-MeOH/DCM) afforded (3a*R*,4*S*,7*R*,7a*S*)-2-((*E*)-4-(methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)but-2-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione as an orange oil with 7% of an inseparable olefinic impurity. Run 1: 66.4 mg, 63% yield; Run 2: 66.4 mg, 63% yield; Run 3: 69.5 mg, 66% yield. **Average 64% yield (±1.7%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.33 (app d, *J* = 4.5 Hz, 4H), 7.30 – 7.22 (m, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.70 (dt, *J* = 15.8, 6.5 Hz, 1H), 5.54 (dt, *J* = 15.4, 6.3 Hz, 1H), 5.27 (dd, *J* = 8.3, 4.8 Hz, 1H), 4.00 (app d, *J* = 6.3 Hz, 2H), 2.95 (app t, *J* = 6.3 Hz, 2H), 2.67 (br s, 2H), 2.57 (br s, 2H), 2.55 – 2.44 (m, 1H), 2.46 – 2.39 (m, 1H), 2.21 – 2.11 (m, 1H), 2.17 (s, 3H), 2.02 – 1.89 (m, 1H), 1.72 – 1.57 (m, 2H), 1.37 – 1.28 (m, 2H), 1.18 (d, *J* = 11.0 Hz, 1H), 1.07 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.55, 160.79, 141.27, 132.03, 128.85, 127.91, 126.82 (q, *J* = 3.8 Hz), 125.98, 125.94, 123.44 (q, *J* = 271.3 Hz), 122.78 (q, *J* = 32.6 Hz), 115.90, 78.50, 59.32, 53.23, 48.74, 42.02, 39.98, 39.88, 36.59, 33.19, 28.12. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.51. HRMS (ESI – TOF ES+) m/z calc'd for $C_{30}H_{33}F_3N_2O_3$ $[M+H]^+$: 527.2477; found 527.2515.

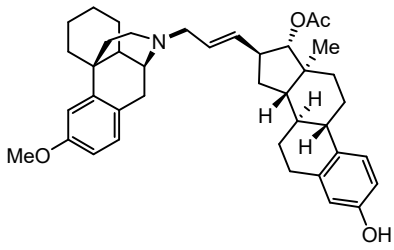


(E)-8-(4-(4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl)but-2-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (76): 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine-borontrifluoride (72.6 mg, 0.2 mmol, 1 eq) and 8-(but-3-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione (44.3 mg, 0.2 mmol, 1 eq) were reacted according to general procedure 0.2 mL of an 0.50M solution of dibutyl phosphate in toluene (0.50 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (SiO_2, 30% → 40% → 45% → 55% → 65% → 70% EtOAc/DCM eluent) resulted in a greasy solid. The solid was triturated with pentane (5 x 1 mL), dissolved in DCM, and passed through a short plug (SiO_2; 5% MeOH/DCM). The resulting solid was recrystallized via the addition of hot *i*PrOH to a suspension of the solid until dissolution occurred. The resulting solution was allowed to come to room temperature, cooled to 0 ºC, and then cooled to -20 ºC for at least 1 hour. The recrystallized (*E*)-8-(4-(4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl)but-2-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione was collected as off-white crystals. Run 1: 62.8 mg, 61% yield; Run 2: 63.8 mg, 62% yield; Run 3: 58.7 mg, 57% yield. **Average 60% yield (±2.6%)**. ^{1}H NMR (*Note*: d1 relaxation delay set to 60 seconds to account for the slow relaxation of the protons associated with one set of piperazine $(–CH_2–)_2$ multiplets from 4.01–3.08 ppm. With lesser delay times, these protons do not integrate to the appropriate amount of nuclides). (500 MHz, Chloroform-*d*) δ 7.48 (app d, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.86 (td, *J* = 7.5, 1.5 Hz, 1H), 5.68 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.60 (dt, *J* = 15.5, 5.6 Hz, 1H), 4.35 (d, *J* = 5.5 Hz, 2H), 4.01 – 3.08 (br m, 4H), 2.99 (app d, *J* = 6.1 Hz, 2H), 2.57 (s, 4H), 2.56 – 2.34 (m, 4H), 1.74 – 1.63 (m, 4H), 1.53 – 1.44 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.91, 160.80, 149.02, 139.99, 134.22, 132.24, 132.21, 130.82, 129.74, 129.16,

129.09, 128.30, 128.07, 128.03, 125.40, 122.83, 60.34, 52.87, 44.89, 40.60, 39.63, 37.67, 24.26. *Note:* Peaks at 52.87 ppm are the superposition of the two piperazinyl carbon signals. HRMS (ESI) m/z calc'd for $C_{30}H_{34}N_4O_2S$ $[M+H]^+$: 515.2436; found 515.2480.

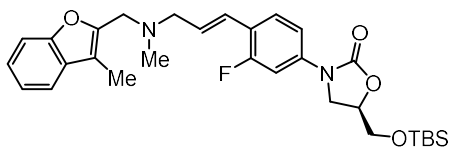


methyl (*E*)-2-acetoxy-4-(3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)prop-1-en-1-yl)benzoate (77): 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-borontrifluoride (41.4 mg, 0.2 mmol, 1.0 eq) and methyl 2-acetoxy-4-allylbenzoate (46.8 mg, 0.2 mmol, 1.0 eq) were reacted according to the general procedure using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 eq), Ma-SOX (3.4 mg, 0.01 mmol, 0.05 eq), and 0.2 mL of a 0.5 M solution of dibutyl phosphate in dioxane (0.5 eq) as a solvent and stirred for 24 h. Purification *via* flash column chromatography (50 mL SiO_2, 0.5% NH_4OH-MeOH/DCM (400 mL)→1% NH_4OH-MeOH/DCM (400 mL)→1.5% NH_4OH-MeOH/DCM (400 mL) eluent) afforded the product as a yellow oil. Run 1: 62.7 mg, 84% yield; Run 2: 63.1 mg, 86% yield; Run 3: 62.0 mg, 84% yield. **Average 85% yield (± 1.0%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 5.1 Hz, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.6 Hz, 1H), 3.86 (s, 3H), 3.60 (s, 2H), 3.36 (d, *J* = 6.6 Hz, 2H), 2.92 (app t, *J* = 5.5 Hz, 2H), 2.85 (app t, *J* = 5.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.83, 164.85, 149.86, 135.18, 133.74, 133.43, 131.32, 131.02, 129.69, 128.77, 125.29, 124.11, 123.23, 122.87, 60.04, 53.17, 52.32, 50.82, 25.55, 21.07. HRMS (ES+) m/z calc'd for $C_{20}H_{22}NO_4S$ $[M+H]+$: 372.1270; found 372.1260.

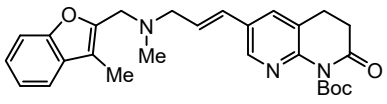


(8*R*,9*S*,13*S*,14*S*,16*S*,17*S*)-3-hydroxy-16-((*E*)-3-((4b*S*,9*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-11-yl)prop-1-en-1-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (78): (4b*S*,8a*S*,9*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epiminoethano)phenanthrene-borontrifluoride (65.0 mg, 0.2 mmol, 1 eq) and (8*R*,9*S*,13*S*,14*S*,16*R*,17*S*)-16-allyl-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (70.9 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (SiO_2, 5% → 20% EtOAc/Hx → 0% → 1% → 2% → 5% →10% MeOH/DCM) afforded the product as a brown solid. Run 1: 79.8 mg, 65% yield; Run 2: 78.8 mg, 65% yield; Run 3: 77.1 mg, 63% yield. **Average 64% yield (±1.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.08 (app t, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 5.89 (dd, *J* = 15.3, 8.5 Hz, 1H), 5.67 (dt, *J* = 14.8, 7.1 Hz, 1H), 4.62 (d, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.58 – 3.40 (m, 3H), 3.11 – 2.91 (m, 3H), 2.86 – 2.72 (m, 2H), 2.72 – 2.63 (m, 1H), 2.44 – 2.30 (m, 2H), 2.28 – 2.16 (m, 1H), 2.17 – 2.08 (m, 2H), 2.06 (s, 3H), 2.01 – 1.90 (m, 1H), 1.82 – 1.61 (m, 4H), 1.58 – 1.16 (m, 13H), 1.09 (qd, *J* = 12.7, 4.0 Hz, 1H), 0.82 (s, 3H).

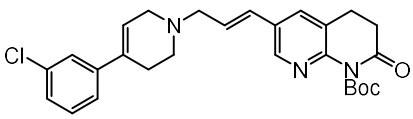
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.47, 159.15, 154.28, 143.53, 139.88, 137.98, 131.56, 129.01, 126.47, 126.24, 119.97, 115.60, 113.00, 111.96, 111.36, 86.62, 57.69, 56.73, 55.41, 48.82, 45.88, 44.18, 43.94, 43.79, 42.33, 39.35, 38.44, 37.00, 36.73, 35.65, 30.49, 29.65, 27.11, 26.18, 26.08, 25.95, 24.34, 21.90, 21.25, 12.68. HRMS (ESI) m/z calc'd for $C_{40}H_{52}NO_4$ $[M+H]^+$: 610.3896; found 610.3889. $[\alpha]^{23}_D$ = +44.51 (c = 0.95, $CHCl_3$).



((*R*,*E*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(3-fluoro-4-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)prop-1-en-1-yl)phenyl)oxazolidin-2-one (79): *N*-methyl-1-(3-methylbenzofuran-2-yl)methanamine-borontrifluoride (48.6 mg, 0.2 mmol, 1.0 eq) and (*R*)-3-(4-allyl-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one (73.1 mg, 0.2 mmol, 1.0 eq) were reacted according to general procedure using 0.2 mL of an 0.25M solution of dibutyl phosphate in dioxane (0.25 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (SiO_2, 0% → 0.25% → 0.5% → 0.75% → 1.0% → 1.5% NH_4OH-MeOH/DCM) afforded ((*R*,*E*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(3-fluoro-4-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)prop-1-en-1-yl)phenyl)oxazolidin-2-one as a pale yellow. Run 1: 78.7 mg, 73% yield; Run 2: 81.9 mg, 76% yield; Run 3: 84.0 mg, 78% yield. **Average 76% yield (±2.5%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.39 (m, 4H), 7.29 – 7.17 (m, 3H), 6.66 (d, *J* = 16.1 Hz, 1H), 6.35 (dt, *J* = 16.0, 6.7 Hz, 1H), 4.71 – 4.63 (m, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.96 – 3.85 (m, 2H), 3.79 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.71 (s, 2H), 3.27 (app d, *J* = 6.8 Hz, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 0.84 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.25 (d, *J* = 248.2 Hz), 154.50, 154.39, 150.19, 138.76 (d, *J* = 11.1 Hz), 129.94, 129.03 (d, *J* = 4.3 Hz), 127.63 (d, *J* = 5.2 Hz), 124.69 (d, *J* = 3.0 Hz), 124.11, 122.24, 120.26 (d, *J* = 12.9 Hz), 119.24, 113.66, 113.35 (d, *J* = 3.0 Hz), 111.27, 105.74 (d, *J* = 28.2 Hz), 72.57, 63.57, 60.14, 51.86, 46.67, 42.46, 25.82, 18.28, 8.23, -5.28, -5.34. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -116.19 (dd, *J* = 12.0, 7.5 Hz). HRMS (ESI – TOF ES+) m/z calc'd for $C_{30}H_{39}FN_2O_2Si$ $[M+H]^+$: 539.2697; found 539.2744. $[\alpha]^{24}_D$ = -31.96 (c = 1.00, $CHCl_3$).

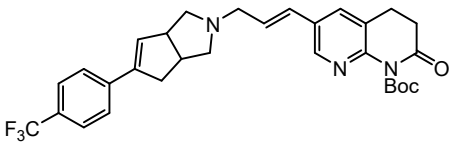


***tert*-butyl (*E*)-6-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)prop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxylate (80)**: *N*-methyl-1-(3-methylbenzofuran-2-yl)methanamine-borontrifluoride (48.6 mg, 0.2 mmol, 1 eq) and *tert*-butyl 6-allyl-2-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (57.7 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in toluene (0.5 eq) as a solvent and stirred for 48 h. Purification *via* flash column chromatography (SiO_2, 75% EtOAc/Hx → 0% → 1% → 2% → 5% → 10% → 25% MeOH/DCM) afforded the product as a yellow solid. Run 1: 72.6 mg, 79% yield; Run 2: 76.3 mg, 83% yield; Run 3: 75.2 mg, 81% yield. **Average 81% yield (±2.1%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.49 – 7.42 (m, 3H), 7.28 – 7.17 (m, 2H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.6 Hz, 1H), 3.71 (s, 2H), 3.26 (d, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 2.22 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.51, 154.34, 150.71, 150.03, 149.62, 145.29, 132.82, 129.89, 128.85, 128.61, 128.49, 124.17, 122.29, 119.25, 119.05, 113.70, 111.25, 85.40, 59.76, 51.95, 42.61, 31.12, 27.79, 23.92, 8.26. HRMS (ESI) m/z calc'd for $C_{27}H_{32}N_3O_4$ $[M+H]^+$: 462.2393; found 462.2396.



tert-butyl (*E*)-6-(3-(4-(3-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl)prop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxylate (81): 4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridine-borontrifluoride (52.3 mg, 0.2 mmol, 1 eq) and *tert*-butyl 6-allyl-2-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (57.7 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred

for 72 h. Purification *via* flash column chromatography (SiO_2, 75% EtOAc/Hx → 0% → 1% → 2% → 5% → 10% → 25% MeOH/DCM) afforded the product as a brown solid. Run 1: 82.9 mg, 86% yield; Run 2: 82.7 mg, 86% yield; Run 3: 84.6 mg, 88% yield. **Average 87% yield (±1.1%)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 7.55 (s, 1H), 7.36 (s, 1H), 7.28 – 7.16 (m, 3H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.2, 6.7 Hz, 1H), 6.20 – 6.03 (m, 1H), 3.29 (d, *J* = 6.7 Hz, 2H), 3.25 – 3.17 (m, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 5.7 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.64 – 2.52 (m, 2H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.49, 150.70, 149.72, 145.36, 142.74, 134.43, 134.29, 132.93, 129.66, 128.83, 128.78, 128.01, 127.18, 125.31, 123.22, 123.02, 119.10, 85.43, 60.49, 53.24, 50.07, 31.13, 28.09, 27.80, 23.96. HRMS (ESI) m/z calc'd for $C_{27}H_{31}N_3O_3Cl$ $[M+H]^+$: 480.2054; found 480.2047.

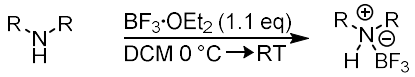


tert-butyl (*E*)-6-(3-(4-(3-chlorophenyl)-3,6-dihydropyridin-1(2*H*)-yl)prop-1-en-1-yl)-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxylate (82): 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole-borontrifluoride (64.2 mg, 0.2 mmol, 1 eq) and *tert*-butyl 6-allyl-2-oxo-3,4-dihydroquinoline-1(2H)-carboxylate (57.7 mg, 0.2 mmol, 1 eq) were reacted according to the general procedure using 0.2 mL of a 0.5M solution of dibutylphosphate in dioxane (0.5 eq) as a solvent and stirred for 72 h. Purification *via* flash column chromatography (SiO_2, 75% EtOAc/Hx → 0% → 1% → 2% → 5% → 10% → 20% MeOH/DCM) afforded the product as a brown solid. Run 1: 95.6 mg, 89% yield; Run 2: 90.8 mg, 84% yield; Run 3: 92.2 mg, 85% yield. **Average 86% yield (±2.3%)**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.48 (m, 3H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.8, 6.5 Hz, 1H), 6.20 – 6.14 (m, 1H), 3.56 – 3.46 (m, 1H), 3.26 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.20 (dd, *J* = 13.5, 6.6

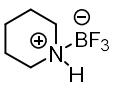
Hz, 1H), 3.12 – 2.96 (m, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.82 (d, J = 7.7 Hz, 1H), 2.79 (d, J = 8.6 Hz, 1H), 2.69 (t, J = 7.4 Hz, 2H), 2.59 (app d, J = 15.6 Hz, 1H), 2.50 (dd, J = 9.3, 4.3 Hz, 1H), 2.45 (dd, J = 9.2, 4.7 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.49, 150.72, 149.62, 145.29, 140.96, 139.69, 132.89, 130.43, 129.01 (q, J = 33.0 Hz), 128.95, 128.86, 127.76, 126.11, 125.31 (q, J = 3.8 Hz), 124.37 (q, J = 271.7 Hz), 119.04, 85.40, 62.55, 59.85, 58.20, 50.85, 40.01, 39.70, 31.13, 27.79, 23.93. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.32. HRMS (ESI) m/z calc'd for $C_{30}H_{33}N_3O_3F_3$ $[M+H]^+$: 540.2474; found 540.2465.

2.4.4 Synthesis of Starting Materials

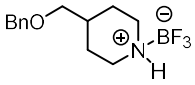
Scheme 2.2: General Synthesis of Amine-BF_3 salts



A solution of the amine in DCM or THEF (0.25 M) was cooled to 0 °C and BF_3•OEt_2 (1.1. eq) was added. After stirring for 30 min at 0 °C, the solution was allowed to warm up to room temperature and allowed to stir until full consumption of the amine was observed by TLC (1-16 h). The solution was then concentrated under reduced pressure and purified by column chromatography.

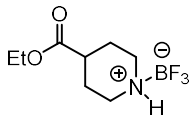


piperidine-borontrifluoride: Prepared according to literature procedure

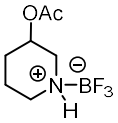


4-((benzyloxy)methyl)piperidine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of 4-((benzyloxy)methyl)piperidine (616 mg, 3 mmol, 1 eq) in DCM (12 mL, 0.25M) was added BF_3•OEt_2 (0.41 mL, 3.3 mmol, 1.1.

eq). Purification by column chromatography (SiO_2, 10% → 20% → 100% EtOAc/Hx) afforded 4-((benzyloxy)methyl)piperidine-borontrifluoride complex as a white solid (273 mg, 1 mmol, 33% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.33 (m, 2H), 7.33 – 7.28 (m, 3H), 4.50 (s, 2H), 3.58 (br s, 1H), 3.46 – 3.39 (m, 2H), 3.34 (d, *J* = 6.2 Hz, 2H), 2.73 (app qd, *J* = 13.7, 2.9 Hz, 2H), 2.00 (d, *J* = 14.1 Hz, 2H), 1.93 – 1.78 (m, 1H), 1.34 (qd, *J* = 14.2, 4.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.20, 128.59, 127.89, 127.71, 74.18, 73.37, 45.62, 35.24, 28.03. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.55 (q, *J* = 15.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{13}H_{18}ONBF_3$ [M—H]$^-$: 272.1428; found 272.1432.

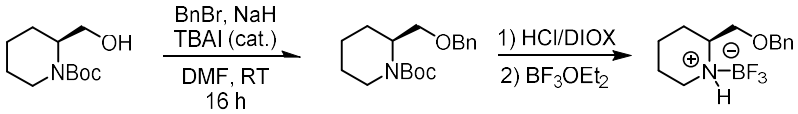


Ethyl piperidine-4-carboxylate-borontrifluoride: Following the general BF3 complexation procedure to a solution of ethyl piperidine-4-carboxylate (0.56 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded ethyl piperidine-4-carboxylate-borontrifluoride as a white solid (715 mg, 3.18 mmol, 64% yield 8.1:1 d.r.). The diastereomeric ratio was determined by ^{19}F NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.15 (q, *J* = 7.1 Hz, 2.2H), 3.99 (br s, 1.1H), 3.44 (d, *J* = 13.7 Hz, 2H), 3.23 (d, *J* = 13.1 Hz, 0.23H), 2.90 (app dq, *J* = 11.7 Hz, 0.26H), 2.74 (qd, *J* = 13.7, 2.9 Hz, 2H), 2.49 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.30 (d, *J* = 14.4 Hz, 0.28H), 2.18 (d, *J* = 13.0 Hz, 2.1H), 1.93 – 1.79 (m, 0.28H), 1.74 (qd, *J* = 13.2, 3.3 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.55, 173.18, 61.32, 61.25, 44.99, 42.92, 39.73, 36.15, 26.75, 25.37, 14.27, 14.21. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.64 – -156.90 (m), -157.35 (q, *J* = 15.0 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_8H_{14}BNO_2F_3$ [M—H]$^-$: 224.1070; found 224.1067.



3-acetoxypiperidine-borontrifluoride Following the general BF3 complexation procedure to a solution of 3-acetoxypiperidine (716 mg, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded (*S*)-2-((benzyloxy)methyl)piperidine-borontrifluoride as a colorless oil (322 mg, 1.18 mmol, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 – 5.10 (m, 1H), 4.06 (br s, 1H), 3.50 – 3.36 (m, 2H), 2.91 (ddd, *J* = 13.9, 11.8, 1.8 Hz 1H), 2.78 (app qd, *J* = 13.4, 3.4 Hz, 1H), 2.13 (s, 3H), 2.07–2.01 (m, 1H), 1.92 (qt, *J* = 13.6, 4.1 Hz, 1H), 1.84–1.77 (m, 1H), 1.72–1.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.69, 65.51, 48.66, 45.45, 26.56, 21.09, 19.08. ^{19}F NMR (376 MHz, $CDCl_3$) δ -158.56 (q, *J* = 14.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_7H_{12}NO_2BF_3$ $[M—H]^-$: 210.0919; found 210.0918.

Scheme 2.3: Synthesis of (*S*)-2-((benzyloxy)methyl)piperidine-borontrifluoride

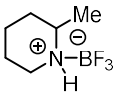


Synthesis of tert-*butyl (*S*)-2-((benzyloxy)methyl)piperidine-1-carboxylate*: A flask was charged with tert-butyl (S)-2-(hydroxymethyl)piperidine-1-carboxylate (887.2 mg, 4.1 mmol, 1 eq) and tetrabutylammonium iodide (61 mg, 0.17 mmol, 0.04 eq). DMF (20 mL, 0.2 M) was added under nitrogen, followed by benzyl bromide (0.98 mL, 8.2 mmol, 2 eq). The solution was cooled to 0 °C and sodium hydride (200 mg, 8.2 mmol, 2 eq) was added. The solution was allowed to warm to room temperature while stirring overnight. After 16 hours, the solution was quenched with a saturated solution of NH_4Cl. The organic layer was extracted with DCM (1x) and washed with water (1x), then brine (1x). The crude mixture was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification *via* column chromatography (SiO2, 10% → 30%

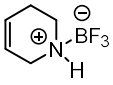
EtOAc/Hx) afforded *tert*-butyl (*S*)-2-((benzyloxy)methyl)piperidine-1-carboxylate as a clear oil (1.32 g, 4.1 mmol, >99% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.43 (br s, 1H), 3.97 (br d, *J* = 13.4 Hz, 1H), 3.54 (app d, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 12.3 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.64 – 1.53 (m, 3H), 1.52 – 1.33 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.37, 138.58, 128.46, 127.65, 127.64, 79.42, 72.92, 68.02, 49.54, 39.99, 28.59, 25.45, 25.34, 19.37. HRMS (ESI) m/z calc'd for $C_{18}H_{27}NONa$ $[M+Na]^+$: 328.1889; found 328.1878. $[\alpha]^{22}_D$ = -38.91 (c = 1.08, $CHCl_3$).

*Synthesis of (*S*)-2-((benzyloxy)methyl)piperidine-borontrifluoride*: A flask was charged with *tert*-butyl (*S*)-2-((benzyloxy)methyl)piperidine-1-carboxylate (1.32 g, 4.1 mmol, 1 eq), dioxane (2.9 mL, 1.4 M) and 4M HCl in dioxane (2.9 mL, 11.3 mmol, 2.75 eq). The mixture was allowed to stir overnight, forming a white precipitate. The crude mixture was concentrated under reduced pressure and mixed with Et_2O to precipitate the amine hydrochloride salt. The salt was filtered and triturated with Et_2O. The precipitate was dissolved in DCM and basified with a saturated K_2CO_3 in H_2O to a pH of 14. The layers were seperated and the aqueous layer was extracted with DCM two times. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford (S)-2-((benzyloxy)methyl)piperidine (698.8 mg, 3.4 mmol, 83% yield). The crude 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine was used directly in the next step with no other purification. Following the general BF3 complexation procedure to a solution of (S)-2-((benzyloxy)methyl)piperidine (613 mg, 3 mmol, 1 eq) in tetrahydrofuran (12 mL, 0.25M) was added BF_3•OEt_2 (0.41 mL, 3.3 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded (*S*)-2-((benzyloxy)methyl)piperidine-borontrifluoride as a colorless oil (322 mg,

1.18 mmol, 39% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.93 (br s, 1H), 3.91 (dd, *J* = 9.7, 3.5, 1H) 3.50 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.36 – 3.22 (m, 2H), 2.98 – 2.82 (m, 1H), 1.96 – 1.86 (m, 2H), 1.85 – 1.67 (m, 2H), 1.53 – 1.39 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.59, 128.66, 128.27, 128.19, 73.47, 68.73, 55.53, 44.84, 26.78, 23.36, 21.62. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -151.77 (q, *J* = 16.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{13}H_{18}ONBF_3$ $[M—H]^-$: 272.1428; found 272.1432. $[\alpha]^{22}_D$ = +10.50 (c = 1.10, $CHCl_3$).



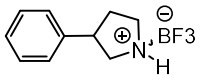
2-methylpiperidine-borontrifluoride: Following the general BF3 complexation to a solution of 2-methylpiperidine (0.59 mL, 5 mmol, 1 eq) in tetrahydrofuran (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded 2-methylpiperidine-borontrifluoride as a cloudy colorless oil (725 mg, 4.34 mmol, 87% yield, 2.9:1 d.r.). The diastereomeric ratio was determined by ^{19}F NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.92 (br s, 0.3 H), 3.70 – 3.58 (m, 0.3 H), 3.50 (d, *J* = 13.7 Hz, 1H), 3.34 (br s, 1H), 3.15 – 2.92 (m, 1.6H), 2.67 (dtd, *J* = 16.3, 11.7, 2.9 Hz, 1H), 1.95 – 1.26 (m, 11.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.95, 49.90, 47.01 (q, J_{CF} = 2.8 Hz), 40.44, 33.87, 30.72, 24.46, 24.36, 23.03, ^{13}C NMR (126 MHz, Chloroform-*d*) δ 47.00 (q, *J* = 3.4 Hz), 20.49 (q, J_{CF}= 2.7 Hz), 17.73, 13.25. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -149.56 (q, *J* = 17.3 Hz), -151.79 (br s). HRMS (ESI) m/z calc'd for $C_6H_{12}NBF_3$ $[M—H]^-$: 166.10; found 166.10.



1,2,3,6-tetrahydropyridine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 1,2,3,6-tetrahydropyridine (0.45 mL, 5 mmol, 1 eq) in tetrahydrofuran (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq).

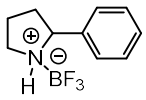
Purification by column chromatography (SiO_2, 10% → 20 → 30% EtOAc/Hx) afforded 1,2,3,6-tetrahydropyridine-borontrifluoride as a white solid (449 mg, 2.97 mmol, 59% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.98 – 5.90 (m, 1H), 5.81 – 5.73 (m, 1H), 3.76 – 3.49 (m, 4H), 2.93 (app qd, *J* = 11.9, 5.2 Hz, 1H), 2.49 – 2.36 (m, 1H), 2.37 – 2.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 125.54, 122.31, 44.02, 42.56, 23.57. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -158.22 (q, *J* = 14.9 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_5H_8NBF_3$ $[M—H]^-$: 150.0696; found 150.0704. *Experimental Note: when purchased from Enamine the Pd-reaction worked well. Other vendors gave variable results.*

pyrrolidine-borontrifluoride: Following the general BF_3 complexation protocol, to a solution of pyrrolidine (0.41 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 20% → 60% EtOAc/Hx) afforded pyrrolidine-borontrifluoride as a white solid (616mg, 4.43 mmol, 89% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.28 (br s, 1H), 3.35 – 3.21 (m, 2H), 3.21 – 3.11 (m, 2H), 2.11 – 1.99 (m, 2H), 1.99 – 1.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.42, 24.57. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.53 (q, *J* = 16.7, 16.1, 15.1 Hz). HRMS (ESI-TOF EI–) m/z: $[M—H]^-$ calc'd for $C_4H_8BNF_3$ $[M—H]^-$: 138.072; found 138.074.

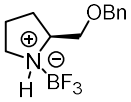


3-phenylpyrrolidine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of 3-phenylpyrrolidine (0.29 mL, 2 mmol, 1 eq) in DCM (8 mL, 0.25M) was added BF_3•OEt_2 (0.27 mL, 2.2 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 20% → 30 → 40 → 50% EtOAc/Hx) afforded 3-phenylpyrrolidine-borontrifluoride as a white solid (295.6 mg, 1.37 mmol, 69% yield as a mixture

of diastereomers). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.32 (m, 2H), 7.26 (m, 3H), 4.65 (br s, 1H), 3.74 – 3.46 (m, 2H), 3.46 – 3.29 (m, 2H), 3.27 – 3.10 (m, 1H), 2.55 – 2.32 (m, 1H), 2.26 – 2.02 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.71, 138.86, 129.22, 129.12, 127.71, 127.66, 127.22, 126.96, 53.55, 53.48, 47.78, 47.48, 44.59, 43.31, 32.86, 32.39. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.49 (q, *J* = 15.3 Hz), -156.60 (q, *J* = 15.5 Hz). HRMS (ESI) m/z calc'd for $C_{10}H_{13}NNaBF_3$ $[M+Na]^+$: 238.0991; found 238.0990.

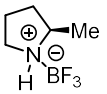


2-phenylpyrrolidine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of 2-phenylpyrrolidine (0.75 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 2.2 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded 2-phenylpyrrolidine-borontrifluoride as a pink solid (946 mg, 4.40 mmol, 88% yield) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 5H), 4.63 – 4.51 (m, 1H), 4.24 (br s, 1H), 3.44 – 3.26 (m, 2H), 2.49 – 2.35 (m, 1H), 2.23 – 2.06 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.58, 129.43, 129.13, 127.17, 64.22, 48.71, 33.46, 25.45. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -154.60 (q, *J* = 15.7 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{12}BNF_3$ $[M—H]^-$: 214.1015; found 214.1019.

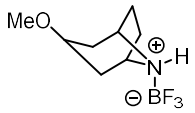


(*S*)-2-((benzyloxy)methyl)pyrrolidine-borontrifluoride: Following the general BF3 complexation procedure to a solution of (*S*)-2-((benzyloxy)methyl)pyrrolidine (991 mg, 5.18 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.7 mL, 5.7 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 15% → 20 → 30% EtOAc/Hx) afforded (*S*)-2-((benzyloxy)methyl)pyrrolidine-borontriflouride as a white solid (639 mg, 2.47 mmol, 48% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 5H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.63

(br, s, 1H), 4.50 (d, J = 11.7 Hz, 1H), 3.87 (dd, J = 10.0, 3.4 Hz, 1H), 3.75 – 3.65 (m, 1H), 3.56 (d, J = 10, 1.2 Hz, 1H), 3.24 (q, J = 6.9 Hz, 2H), 2.15 – 1.85 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.16, 128.79, 128.37, 128.03, 73.64, 68.14, 59.82, 48.63, 28.39, 24.84. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -155.92 (q, J = 16.0 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{12}H_{16}BNOF_3$ $[M—H]^-$: 258.1277; found 258.1278. $[\alpha]^{22}_D$ = -12.86 (c = 1.10, $CHCl_3$).

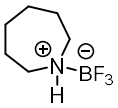


(*R*)-2-methylpyrrolidine-borontrifluoride: Following the general BF3 complexation procedure to a solution of (*R*)-2-methylpyrrolidine (0.3 mL, 3 mmol, 1 eq) in DCM (12 mL, 0.25M) was added BF_3•OEt_2 (0.4 mL, 3.3 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 20% → 30 → 50% EtOAc/Hx) afforded (*R*)-2-methylpyrrolidine-borontrifluoride as a colorless oil (425 mg, 2.78 mmol, 93% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.04 – 3.70 (m, 1H), 3.65 – 3.51 (m, 1H), 3.34 – 3.24 (m, 1H), 3.25 – 3.13 (m, 1H), 2.18 (app p, J = 6.6 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.57 (app dq, J = 12.9, 8.0 Hz, 1H), 1.40 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.14, 48.34, 33.39, 24.00, 19.73. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -154.61 – -155.26 (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_5H_{10}BNF_3$ $[M—H]^-$: 152.0858; found 152.0862. $[\alpha]^{22}_D$ = -14.24 (c = 1.06, $CHCl_3$).

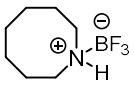


(1R,5S)-3-methoxy-8-azabicyclo[3.2.1]octane-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of (1R,5S)-3-methoxy-8-azabicyclo[3.2.1]octane (511.9 mg, 3.63 mmol, 1 eq) in DCM (15 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 30% → 50% EtOAc/Hx) afforded (1R,5S)-3-methoxy-8-azabicyclo[3.2.1]octane-borontrifluoride as a white solid (360 mg, 1.72 mmol, 48% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.92 (m, 2H),

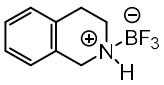
3.85 (br s, 1H), 3.50 (app t, J = 4.9 Hz, 1H), 3.29 (s, 3H), 2.24 – 2.11 (m, 6H), 1.97 (dt, J = 15.7, 4.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 72.49, 56.71, 55.51, 36.35, 26.41. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -153.90 (q, J = 17.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_8H_{14}NBF_3$ $[M—H]^-$: 208.1115; found 208.1125.



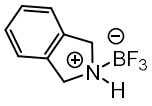
azepane-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of azepane (0.56 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded azepane-borontrifluoride as a white solid (734 mg, 4.39 mmol, 88% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.90 (br s, 1H), 3.44 – 3.32 (m, 2H), 2.94 – 2.81 (m, 2H), 1.99 – 1.88 (m, 2H), 1.85 – 1.60 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.80, 26.84, 26.40. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.91 (q, J = 16.2 Hz). HRMS (ESI-TOF EI–) m/z: $[M—H]^-$ calc'd for $C_6H_{12}BNF_3$ $[M—H]^-$: 166.1009; found 166.1010.



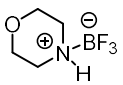
azocane-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of azocane (0.50 mL, 4 mmol, 1 eq) in DCM (16 mL, 0.25M) was added BF_3•OEt_2 (0.54 mL, 4.4 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded azocane-borontrifluoride complex as a white solid (338.1 mg, 1.87 mmol, 47% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.56 (br s, 1H), 3.40 – 3.30 (m, 2H), 2.93 – 2.81 (m, 2H), 1.97 – 1.85 (m, 2H), 1.83 – 1.53 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.27, 26.55, 25.37, 24.63. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.64 (q, J = 15.4 Hz). HRMS (ESI-TOF EI-) m/z calc'd for $C_7H_{14}BNF_3$ $[M—H]^-$: 180.1171; found 180.1174.



1,2,3,4-tetrahydroisoquinoline-borontrifluoride: Following the general BF_3 complexation procedure to a solution of 1,2,3,4-tetrahydroisoquinoline (0.63 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 10% → 20% → 25% EtOAc/Hx) afforded 1,2,3,4-tetrahydroisoquinoline-borontrifluoride as a white solid (728 mg, 3.62 mmol, 75% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.22 (m, 2H), 7.19 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.11 (dd, *J* = 7.0, 1.8 Hz, 1H), 4.30 (dd, *J* = 16.4, 3.2 Hz, 1H), 4.18 (dd, *J* = 16.4, 11.2 Hz, 1H), 3.93 (br s, 1H), 3.77 – 3.66 (m, 1H), 3.19 – 2.98 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.23, 129.48, 129.17, 128.22, 127.39, 126.90, 47.09, 43.52, 26.92. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.74 (q, *J* = 14.4 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_9H_{10}BNF_3$ $[M—H]^-$: 200.0853; found 200.0850.

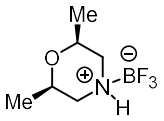


isoindoline-borontrifluoride: Following the general BF_3 complexation procedure to a solution of isoindoline (595.8 mg, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added and BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (20% → 60% EtOAc/Hx) afforded isoindoline-borontrifluoride as a white solid (717 mg, 3.83 mmol, 77% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 4H), 4.91 (br s, 1H), 4.65 – 4.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.40, 128.87, 122.89, 52.87. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.01 (q, *J* = 14.2 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_8H_8NBF_3$ $[M—H]^-$: 186.0696; found 186.0704.

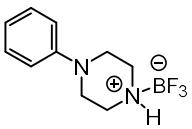


morpholine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of morpholine (0.43 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added

BF_3•OEt_2 (0.68 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 40%→50→60% EtOAc/Hx) afforded morpholine boron-trifluoride as a white solid (721mg, 4.65 mmol, 93% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.12 (br s, 1H), 4.06 (dd, *J* = 12.9, 3.5 Hz, 2H), 3.65 (td, *J* = 12.5, 2.3 Hz, 2H), 3.19 (d, *J* = 13.4 Hz, 2H), 3.05 (dtd, *J* = 14.3, 11.4, 3.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 65.44, 45.03. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.34 (q, *J* = 15.0 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_4H_8BNOF_3$ [M—H]$^-$: 154.0646; found 150.0655.

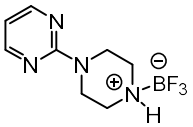


(2*R*,6*S*)-2,6-dimethylmorpholine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of (2*R*,6*S*)-2,6-dimethylmorpholine (0.62 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 22 mmol, 1.1 eq). Purification by column chromatography (SiO_2, 60% EtOAc/Hx) afforded of (2*R*,6*S*)-2,6-dimethylmorpholine-borontrifluoride as a white solid (868 mg, 4.74 mmol, 95% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.01 (br s, 1H), 3.77 – 3.59 (m, 2H), 3.15 (app d, *J* = 14.1 Hz, 2H), 2.55 (ddd, *J* = 12.5, 12.0, 11.5 Hz, 2H), 1.24 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.09, 49.51, 18.83^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.62 (q, *J* = 14.6 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_6H_{12}BNOF_3$ [M—H]$^-$: 182.0964; found 182.0969.

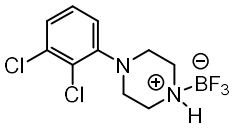


1-phenylpiperazine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 1-phenylpiperazine (0.75 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 30%→70% EtOAc/Hx) afforded 1-phenylpiperazine-borontrifluoride as a white solid (994 mg, 4.32 mmol, 86% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (td, *J* =

7.9, 3.1 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 13.8 Hz, 2H), 3.78 – 3.66 (br s, 1H), 3.44 (app d, *J* = 13.1 Hz, 2H), 3.16 (dtd, *J* = 12.7, 12.3, 2.9 Hz, 2H), 2.92 (td, *J* = 12.7, 2.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.15, 129.58, 121.83, 117.19, 48.72, 45.24). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.31 (q, *J* = 14.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{13}BN_2F_3$ [M—H]$^-$: 229.1124; found 229.1128.



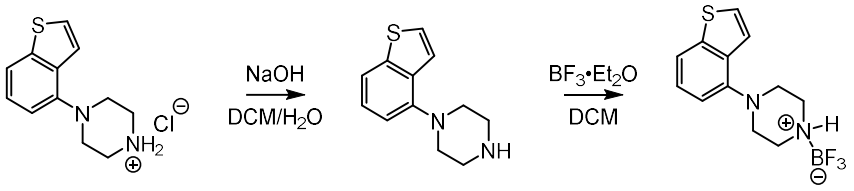
2-(piperazin-1-yl)pyrimidine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 2-(piperazin-1-yl)pyrimidine (821 mg, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 30%→60%→100% EtOAc/Hx) afforded 2-(piperazin-1-yl)pyrimidine-borontrifluoride as a white solid (742 mg, 3.20 mmol, 64% yield). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.41 (d, *J* = 4.7 Hz, 2H), 7.30 (br s, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 4.63 (d, *J* = 14.4 Hz, 2H), 3.16 (d, *J* = 13.2 Hz, 2H), 3.09 (ddd, *J* = 13.6, 12.8, 2.9 Hz, 2H), 2.63 (dtd, *J* = 13.5, 11.3, 3.4 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 160.93, 158.06, 111.05, 43.61, 41.03. ^{19}F NMR (471 MHz, DMSO-*d*$_6$) δ -155.23 (q, *J* = 17.4 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_8H_{11}BN_4F_3$ [M—H]$^-$: 231.1029; found 231.1032.



1-(2,3-dichlorophenyl)piperazine-borontrifluoride: Following the general BF_3 complexation procedure to a solution of 1-(2,3-dichlorophenyl)piperazine (1.16 g, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 20%→30→40%→50% EtOAc/Hx) afforded 1-(2,3-dichlorophenyl)piperazine-borontrifluoride as a white solid (889 mg, 2.97 mmol, 59% yield). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.39 – 7.29

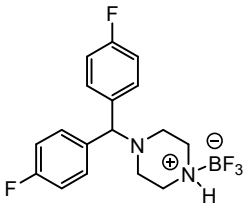
(m, 2H), 7.21 (br s, 1H), 7.17 (dd, *J* = 7.0, 2.5 Hz), 3.33 (d, *J* = 12.2 Hz 2H), 3.17 (d, *J* = 13.3 Hz, 2H), 2.92 (td, *J* = 12.2, 2.1 Hz, 2H), 2.83 (dddd, *J* = 12.3, 11.8, 11.3, 1.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 150.18, 132.72, 128.60, 126.14, 125.04, 119.61, 48.62, 44.16. ^{19}F NMR (471 MHz, DMSO-d_6) δ -155.34 (q, *J* = 17.2 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{11}N_2BCl_2F_3$ $[M—H]^-$: 297.0339; found 297.0344.

Scheme 2.4: Synthesis of 1-(benzo[b]thiophen-4-yl)piperazine-borontrifluoride

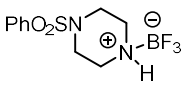


Synthesis of 1-(benzo[b]thiophen-4-yl)piperazine-borontrifluoride: To a separatory funnel was added 4-(benzo[*b*]thiophen-4-yl)piperazin-1-ium chloride (2.5 g, 10 mmol, 1 eq), DCM (100 mL), H_2O (30 mL) and 1 M NaOH in H_2O (30 mL). The contents were mixed, layers were separated, and the aqueous layer was washed with DCM (3 x 30 mL). The combined organic layers were washed with H_2O (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure to afford 1-(benzo[b]thiophen-4-yl)piperazine (2.3 g, 10 mmol, >99% yield) as a yellow oil that was used without further purification. Following the general BF_3 complexation protocol, to a solution of 1-(benzo[b]thiophen-4-yl)piperazine (2.3 g, 10 mmol, 1 eq) in DCM (40 mL, 0.25M) was added BF_3•OEt_2 (1.35 mL, 11 mmol, 1.1 eq). Purification *via* plug (SiO_2, DCM) afforded 1-(benzo[b]thiophen-4-yl)piperazine-borontrifluoride as a white solid (2.3 g, 8.1 mmol, 81% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 5.5 Hz, 1H), 7.35 (d, *J* = 5.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.83 (br s, 1H), 3.63 (d, *J* = 13.3 Hz, 2H), 3.46 (d, *J* = 12.4 Hz, 2H), 3.30 (qd, *J* =

12.1, 2.9 Hz, 2H), 3.06 – 2.97 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.72, 141.60, 134.32, 126.43, 125.08, 121.12, 118.75, 112.85, 51.07, 45.66. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.26 (q, *J* = 11.6 Hz). HRMS (ESI-TOF ES–) m/z calc'd for $C_{12}H_{14}BF_3N_2S$ [M—H]$^-$: 285.0959; found 285.0844.

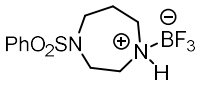


1-(bis(4-fluorophenyl)methyl)piperazine-borontrifluoride: Following the general BF3 complexation procedure to a solution of 1-(bis(4-fluorophenyl)methyl)piperazine (1.44 g, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•Oet_2 (0.68 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 20%→40% EtOAc/Hx) afforded 1-(bis(4-fluorophenyl)methyl)piperazine-borontrifluoride as a white solid (1.19 g mg, 3.33mmol, 67% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 8.4, 5.4 Hz), 7.00 (app t *J* = 8.7 Hz, 4H), 4.27 (s, 1H), 3.57 (br s, 1H), 3.23 (d, *J* = 12.9 Hz, 2H), 3.09 – 2.96 (m, 4H), 2.08 (t, *J* = 12.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.23 (d, J_{CF} = 246.8 Hz), 136.94 (d, J_{CF} = 3.3 Hz), 129.23 (d, J_{CF} = 8.0 Hz), 116.01 (d, J_{CF} = 21.3 Hz), 74.19, 50.43, 45.39. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -114.32 – -114.41 (m), -157.22 – -157.53 (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_{17}H_{17}BN_2F_5$ [M—H]$^-$: 355.1399; found 355.1402.

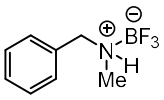


1-(phenylsulfonyl)piperazine-borontrifluoride: Following the general BF_3 complexation procedure to a solution of 1-(phenylsulfonyl)piperazine (3.04 g, 13.5 mmol, 1 eq) in DCM was added BF_3•Oet_2 (1.9 mL, 14.8 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 50% EtOAc/Hx) afforded 1-(phenylsulfonyl)piperazine-borontrifluoride as a white solid (1.40 g, 4.76 mmol, 35% yield). ^{1}H NMR (500 MHz, DMSO-d_6)

δ 7.78 (d, J = 7.5 Hz, 3H), 7.71 (t, J = 7.8 Hz, 2H), 6.95 (br s, 1H), 3.67 (app d, J = 12.3 Hz, 2H), 3.05 (app d, J = 12.4 Hz 2H), 2.69 (dt, J = 15.0, 10.8 Hz, 2H), 2.54 – 2.43 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 134.42, 133.63, 129.62, 127.64, 43.42, 43.27. ^{19}F NMR (471 MHz, DMSO-d_6) δ -155.24 (q, J = 16.6 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{13}BN_2O_2F_3S$ [M—H]$^-$: 293.0743; found 293.0749.

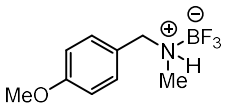


1-(phenylsulfonyl)-1,4-diazepane-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 1-(phenylsulfonyl)-1,4-diazepane (1.2 g, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•Oet_2 (0.68 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 60% EtOAc/Hexanes an eluent) afforded 1-(phenylsulfonyl)-1,4-diazepane-borontrifluoride as a white solid (953 mg, 3.09 mmol, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.83 – 7.78 (m, 2H), 7.73 – 7.69 (m, 1H), 7.67 – 7.61 (m, 2H), 7.06 (br s, 1H), 3.68 (ddd, J = 15.5, 5.9, 2.1 Hz, 1H), 3.38 – 3.14 (m, 5H), 2.73 – 2.60 (m, 2H), 2.05 – 1.97 (m, 1H), 1.89 – 1.78 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 138.03, 133.05, 129.53, 126.78, 47.56, 46.40, 45.25, 44.75, 25.05. ^{19}F NMR (471 MHz, DMSO-d_6) δ -154.49 (q, J = 17.6 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{11}H_{15}BNO_2F_3S$ [M—H]$^-$: 307.0899; found 307.0898.

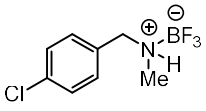


***N*-methylbenzylamine-borontrifluoride:** Following the general BF3 complexation procedure, to a solution of *N*-methylbenzylamine (0.64 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25 M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1 eq). Purification by flash column chromatography (SiO_2, 30%→60% EtOAc/Hx) afforded *N*-methylbenzylamine-borontrifluoride as a white solid (631 mg, 3.34 mmol, 67% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.40 (m, 3H), 7.34 (dd, J = 7.4, 2.0 Hz, 2H), 4.50 (d, J = 13.7, 1H), 3.95

(br s, 1H), 3.59 (dd, *J* = 13.8, 10.6 Hz, 1H), 2.48 (d, *J* = 5.5 Hz, 3H). ^{13}C-NMR (126 MHz, Chloroform-*d*) δ 132.46, 129.68, 129.63, 129.59, 53.73, 32.95. ^{19}F NMR (471 MHz, Chloroform-*d*) -157.15 (q, *J* = 15.1 Hz). HRMS (ESI-TOF EI-) m/z calc'd for $C_8H_{10}BNF_3$ [M—H]$^-$: 188.0858; found 188.0862.

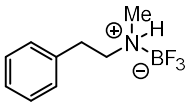


1-(4-methoxyphenyl)-*N*-methylmethanamine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of 1-(4-chlorophenyl)-*N*-methylmethanamine (0.65 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 15%→25%→35% EtOAc/Hx) afforded 1-(4-chlorophenyl)-N-methylmethanamine-borontrifluoride complex as a white solid (869 mg, 3.97 mmol, 79% yield^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.44 (d, *J* = 13.5 Hz, 1H), 3.83 (s, 3H), 3.69 (br s, 1H), 3.54 (dd, *J* = 13.7, 10.5 Hz, 1H), 2.47 (dd, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.55, 131.10, 124.38, 114.96, 55.54, 53.26, 32.81. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.87 – -157.71 (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_9H_{12}BNOF_3$ [M—H]$^-$: 218.0964; found 218.0968.

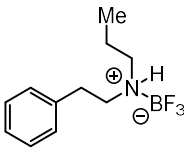


1-(4-chlorophenyl)-*N*-methylmethanamine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of 1-(4-chlorophenyl)-*N*-methylmethanamine (0.72 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 10%→30% EtOAc/Hx) afforded 1-(4-chlorophenyl)-N-methylmethanamine-borontrifluoride as a white solid (638 mg, 2.86 mmol, 57% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 4.44 (dd, *J* = 13.9, 2.4 Hz, 1H), 4.09 (br s, 1H), 3.59 (dd, *J* = 13.9, 10.4 Hz, 1H),

2.47 (dd, J = 6.0, 2.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.83, 131.13, 130.78, 129.87, 52.95, 32.98. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.81 (q, J = 15.0 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_8H_9BNF_3Cl$ [M—H]$^-$: 222.0469; found 222.0472.

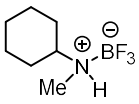


***N*-methyl-2-phenylethan-1-amine-borontrifluoride:** Following the general BF3 complexation procedure, to a solution of *N*-methyl-2-phenylethan-1-amine (2.9 mL, 20 mmol, 1 eq) in DCM (80 mL, 0.25M) was added BF_3•OEt_2 (2.7 mL, 22 mmol, 1.1. eq). Purification by column chromatography (SiO_2, DCM) afforded N-methyl-2-phenylethan-1-amine-borontrifluoride as a white solid (3.18 g, 15.66 mmol, 78% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.25 – 7.21 (m, 2H), 3.61 – 3.51 (m, 1H), 3.37 (s, 1H), 3.17 – 3.06 (m, 1H), 2.99 – 2.89 (m, 2H), 2.61 (d, J = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.75, 129.56, 128.76, 127.82, 50.96, 34.43, 31.85. ^{19}F NMR (471 MHz, Chloroform-*d*) -156.75 – -157.11 (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_9H_{12}BNF_3$ [M—H]$^-$: 202.1015; found 202.1019.

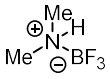


***N*-phenethylpropan-1-amine-borontrifluoride:** Following the general BF3 complexation procedure, to a solution of *N*-phenethylpropan-1-amine (490 mg, 3 mmol, 1 eq) in THF (12 mL, 0.25M) was added BF_3•OEt_2 (0.41 mL, 3.3 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 10% → 20% → 30% EtOAc followed by SiO_2, DCM) afforded *N*-phenethylpropan-1-amine-borontrifluoride as a clear oil (240.8 mg, 1.04 mmol, 35% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (app t, J = 7.5 Hz, 2H), 7.30 (app t, J = 7.4 Hz, 1H), 7.24 (app d, J = 7.0 Hz, 2H), 3.51 – 3.40 (m, 1H), 3.35 – 3.16 (m, 1H), 3.16 – 2.89 (m, 4H), 2.73 – 2.62 (m, 1H), 1.66 – 1.51 (m, 1H), 1.52 – 1.38 (m, 1H), 0.78 (t, J = 7.4 Hz,

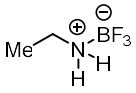
3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.30, 129.49, 129.02, 127.74, 50.61, 49.46, 32.59, 19.43, 10.93. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -154.48 (q, *J* = 15.9 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{11}H_{16}NF_3B$ [M—H]$^-$: 230.1328; found 230.1331.



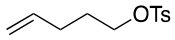
***N*-methylcyclohexanamine-borontrifluoride:** Following the general BF3 complexation procedure, to a solution of *N*-methylcyclohexanamine (0.65 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 10%→20%→30% EtOAc/Hx) afforded *N*-methylcyclohexanamine-borontrifluoride complex as a clear oil (814 mg, 4.50 mmol, 90% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.68 (s, 1H), 3.18 (app t, *J* = 11.6, 1H), 2.54 (d, *J* = 6.4, Hz, 3H), 2.17 – 2.00 (m, 1H), 1.97 – 1.75 (m, 3H), 1.76 – 1.64 (m, 1H), 1.53 (qd, *J* = 12.1, 3.4 Hz, 1H), 1.46 – 1.21 (m, 3H), 1.12 (qt, *J* = 13.0, 3.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 58.57, 30.14, 29.63, 27.53, 25.39, 25.29, 25.19. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -152.61 (q, *J* = 16.7 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_7H_{14}BNF_3$ [M—H]$^-$: 180.1171; found 180.1176.



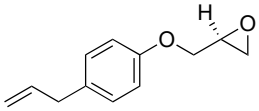
dimethylamine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of dimethylamine (2M solution in THF, 2.5 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 30%→50%→70% EtOAc/Hx) afforded dimethylamine-borontrifluoride complex as a white solid (387 mg, 3.42 mmol, 69% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.89 (br s, 1H), 2.73 – 2.61 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.35. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -159.59 (q, *J* = 14.8 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_2H_6BNF_3$ [M—H]$^-$: 112.0545; found 112.0549.



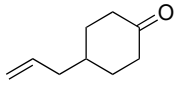
ethanamine-borontrifluoride: Following the general BF3 complexation procedure, to a solution of ethanamine (2M solution in THF, 2.5 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1. eq). Purification by column chromatography (SiO_2, 30%→70% EtOAc/Hx) afforded ethanamine-borontrifluoride complex as a white solid (504 mg, 4.46 mmol, 89% yield^{1}H NMR (500 MHz, DMSO-d_6) δ 6.16 (br s, 2H), 2.61 (app q, J = 7.6, Hz, 2H), 1.09 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 34.96, 13.22. ^{19}F NMR (471 MHz, DMSO-d_6) δ -148.56 (q, J = 19.2 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_2H_6BNF_3$ $[M—H]^-$: 112.0545; found 112.0548.



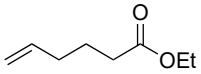
pent-4-en-1-yl 4-methylbenzenesulfonate was prepared according to the literature procedure, and the NMR data matched those reported.



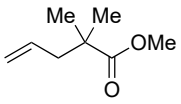
(*S*)-2-((4-allylphenoxy)methyl)oxirane was prepared according to the literature procedure, and spectral data were in accordance to literature values.



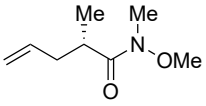
4-allylcyclohexan-1-one was prepared according to the literature procedure, and spectral data were in accordance to literature values.



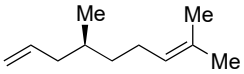
ethyl hex-5-enoate was prepared according to the literature procedure, and spectral data were in accordance to literature values.



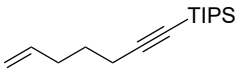
methyl 2,2-dimethylpent-4-enoate was prepared according to the literature procedure, and spectral data were in accordance to literature values.



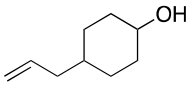
(*S*)-*N*-methoxy-*N*,2-dimethylpent-4-enamide was prepared according to the literature procedure, and spectral data were in accordance to literature values.



(*S*)-4,8-dimethylnona-1,7-diene was prepared according to the literature procedure, and spectral data were in accordance to literature values.

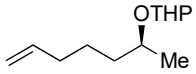


hept-6-en-1-yn-1-yltriisopropylsilane was prepared according to the literature procedure, and spectral data were in accordance to literature values.



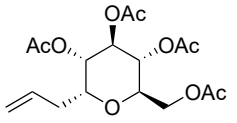
4-allylcyclohexan-1-ol (xx): A solution of 4-allylcyclohexan-1-one[3] (1.56 g, 11.2 mmol, 1 eq) in MeOH (25 mL, 0.45 M) was cooled to 0 °C and $NaBH_4$ (0.65 g, 16.8 mmol, 1.5 eq) was subsequently added portion wise. The reaction was monitored by TLC and allowed to stir overnight from 0 °C to room temperature. The resulting mixture was quenched with sat. NH_4Cl (15 mL) at 0 °C and diluted with Et_2O (15 mL). The aqueous and organic layers were separated, and the aqueous layer was then extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 10% → 20% EtOAc/Hx eluent) afforded the product as a clear oil (1.35 g, 9.63 mmol, 86% yield, 1:0.3 d.r.). The

diastereomeric ratio was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.03 – 4.94 (m, 2H), 3.99 – 3.91 (m, 0.23H), 3.54 (tt, *J* = 10.8, 4.4 Hz, 0.77H), 2.01 (app t, *J* = 6.4 Hz, 0.46H), 1.99 – 1.92 (m, 3H), 1.81 – 1.73 (m, 1.56H), 1.73 – 1.66 (m, 0.52H), 1.59 – 1.47 (m, 1H), 1.47 – 1.33 (m, 1.63H), 1.32 – 1.19 (m, 2.5H), 0.97 (qd, *J* = 13.3, 3.3 Hz, 1.5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 137.57, 137.48, 115.70, 115.65, 71.20, 67.20, 41.19, 40.67,

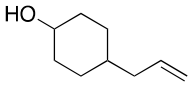


2-(((*S*)-hept-6-en-2-yl)oxy)tetrahydro-2*H*-pyran (xx): Substrate was synthesized according to literature procedure.[9] To a suspension of (*S*)-hept-6-en-2-ol[10] (0.29 g, 2.54 mmol, 1 eq) and 3,4-dihydro-2Hpyran in DCM (5.1 mL, 0.5 M) cooled to 0 °C was added a solution of pyridinium *p*-toluensulfonate (0.06 g, 0.25 mmol, 0.1 eq) in DCM (1 mL). The reaction was allowed to stir from 0 °C to room temperature overnight in which the reaction completion was monitored by TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), the aqueous and organic layers were separated, and the aqueous phase was then extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in* vacuo. Purification *via* flash column chromatography (SiO_2, 0% → 2% EtOAc/pentane eluent) afforded the product as a clear oil (0.5 g, 2.52 mmol, 99% yield, 1:1 d.r.). The diastereomeric ratio was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.81 (app ddq, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 4.97 – 4.91 (m, 1H), 4.72 – 4.68 (m, 0.5H), 4.62 (dd, *J* = 5.1, 2.7 Hz, 0.5H), 3.96 – 3.85 (m, 1H), 3.79 (sext, *J* = 6.3 Hz, 0.5H), 3.72 (sext, *J* = 6.2 Hz, 0.5H), 3.52 – 3.44 (m, 1H), 2.10 – 2.02 (m, 2H), 1.88 – 1.76 (m, 1H), 1.74 – 1.65 (m, 1H), 1.63 – 1.34 (m, 8H), 1.22 (d, *J* = 6.3 Hz, 1.5H), 1.10 (d, *J* = 6.1 Hz, 1.5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 139.10, 138.96, 114.62, 114.52, 98.82, 95.69, 73.92, 71.03, 63.01, 62.59,

37.14, 36.11, 33.97, 33.97, 31.37, 31.36, 25.73, 25.67, 25.35, 24.93, 21.74, 20.26, 19.89, 19.25. HRMS (ASAP+) m/z calc'd for $C_{12}H_{23}O_2$ [M+H]+: 199.1698; found 199.1694.

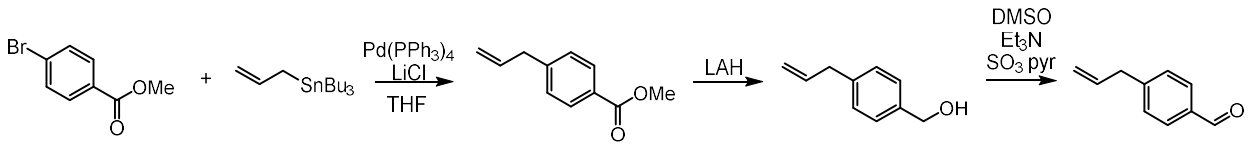


(2*R*,3*R*,4*R*,5*S*,6*R*)-2-(acetoxymethyl)-6-allyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate was prepared according to the literature procedure, and the NMR data matched those reported.



4-allylcyclohexan-1-ol (xx): A solution of 4-allylcyclohexan-1-one[3] (1.56 g, 11.2 mmol, 1 eq) in MeOH (25 mL, 0.45 M) was cooled to 0 °C and $NaBH_4$ (0.65 g, 16.8 mmol, 1.5 eq) was subsequently added portion wise. The reaction was monitored by TLC and allowed to stir overnight from 0 °C to room temperature. The resulting mixture was quenched with sat. NH_4Cl (15 mL) at 0 °C and diluted with Et_2O (15 mL). The aqueous and organic layers were separated, and the aqueous layer was then extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 10% → 20% EtOAc/Hx eluent) afforded the product as a clear oil (1.35 g, 9.63 mmol, 86% yield, 1:0.3 d.r.). The diastereomeric ratio was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.03 – 4.94 (m, 2H), 3.99 – 3.91 (m, 0.23H), 3.54 (tt, *J* = 10.8, 4.4 Hz, 0.77H), 2.01 (app t, *J* = 6.4 Hz, 0.46H), 1.99 – 1.92 (m, 3H), 1.81 – 1.73 (m, 1.56H), 1.73 – 1.66 (m, 0.52H), 1.59 – 1.47 (m, 1H), 1.47 – 1.33 (m, 1.63H), 1.32 – 1.19 (m, 2.5H), 0.97 (qd, *J* = 13.3, 3.3 Hz, 1.5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 137.57, 137.48, 115.70, 115.65, 71.20, 67.20, 41.19, 40.67, 36.82, 36.30, 35.67, 32.35, 31.06, 26.81. HRMS (EI+) m/z calc'd for $C_9H_{16}O$ [M]+: 140.1201; found 140.1201.

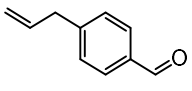
Scheme 2.5: Synthesis of 4-allylbenzaldehyde



Synthesis of methyl-4-allylbenzoate: In a glovebox to a flame-dried round-bottom flask and stir bar was added anhydrous LiCl (4.2 g, 100 mmol, 5 eq). The flask was removed from the glovebox, and to it was added methyl-4-bromobenzoate (4.3 g, 20 mmol, 1 eq). The flask was placed under vacuum and then purged with N_2 (3x). To the flask was added THF (200 mL, 0.1 M) and allyltributylstannane (6.8 mL, 22 mmol, 1.1 eq), and then the solution was stirred and sparged with argon for 15 minutes. The flask was charged with $Pd(PPh_3)_4$ (2.3 g, 2 mmol, 0.1 eq), topped with an oven-dried reflux condenser, and stirred for 22 hours at 80 ºC under argon. The solution was then cooled to room temperature and quenched with a aqueous solution of 9.3% (v/v) NH_4OH (100 mL). The aqueous layer was washed with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under a stream of nitrogen to result in a yellow oil. Purification *via* column chromatography (SiO_2, 0% → 1% → 2% → 4% Et_2O/pentane) followed by a second column chromatography (SiO_2, 1% → 1.5% → 2% → 3% Et_2O/Hx) afforded methyl-4-allylbenzoate as a clear oil at room temperature and white solid at -30 ºC (1.7 g, 9.7 mmol, 49% yield). Spectral data were in accordance to literature values.

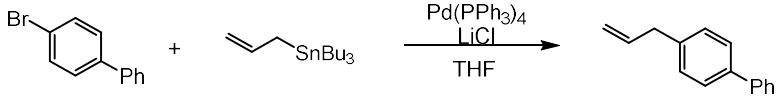
Synthesis of (4-allylphenyl)methanol: A flame dried round-bottom flask was charged with lithium aluminum hydride (854 mg, 22.5 mmol, 3 eq) and THF (44 mL) under inert atmosphere. The solution was cooled to 0 °C. In a separate, pear shaped round-bottom flask, methyl-4-allylbenzoate (1.3 g, 7.5 mmol, 1 eq) was dissolved in THF (22 mL) and taken up in a syringe. The olefin solution was added dropwise to the lithium aluminum hydride solution. After

addition, the solution was allowed to warm to room temperature and stirred for 14.5 hours. Afterwards, the crude mixture was quenched with successive additions of 0.9 mL H_2O, 0.9 mL 15% NaOH in H_2O, and 2.7 mL H_2O and dried over $MgSO_4$. Purification *via* column chromatography (SiO2, 0 → 5 → 30 → 100% EtOAc/Hx) afforded 4-allylphenyl)methanol as a clear oil (856 mg, 5.8 mmol, 77% yield). Spectral data were in accordance to literature values.



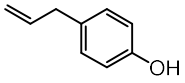
Synthesis of 4-allylbenzaldehyde: An oven dried round-bottom flask was charged with 4-allylphenyl)methanol (851 mg, 5.7 mmol, 1 eq), DMSO (4.1 mmol, 57.4 mmol, 10 eq), Et_3N (4.0 mL, 28.7 mmol, 5 eq) and DCM (57 mL). The solution was cooled to 0 °C and SO_3·pyr was added portion-wise. The solution was stirred at 0 °C for 30 minutes, and then allowed to warm to room temperature and stirred for 16 hours. The crude mixture was diluted with DCM and washed with NaHCO3, 1M HCl and brine. Each aqueous layer was back extracted two times with DCM. The combined organic layers were dried over MgSO4 and concentrated under reduced pressure. Purification *via* column chromatography afforded 4-allylbenzaldehyde as a clear oil. Spectral data were in accordance to literature values

Scheme 2.6: Synthesis of 4-allyl-1,1'-biphenyl

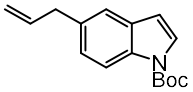


4-allyl-1,1'-biphenyl: A flamed-dried flask was charged with 4-bromo-1,1'-biphenyl (1.2 g, 5 mmol, 1 eq), LiCl (1.1 g, 25 mmol, 5 eq), THF (0.1 M) and finally allyltributylstannane (1.7 mL, 5.5 mmol, 1.1 eq). The solution was stirred and degassed under dry argon for 15 mins. Then, $Pd(PPh_3)_4$ (580 mg, 0.5 mmol, 0.1 eq) was added as a solid and the reaction flask was fitted with

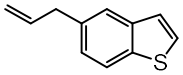
an oven-dried condenser. The reaction was heated in 80 °C oil bath for 22 hours under argon. After cooled down to RT, the reaction was diluted with water and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc 3 times. The organic layers were combined and dried over anhydrous $MgSO_4$. The solid was filtered off and the solvent was removed under reduced pressure. Purification *via* column chromatography (SiO_2, 0 → 5% EtOAc/Hx) afforded 4-allyl-1,1'-biphenyl as a clear oil (525 mg, 2.7 mmol, 54% yield). Spectral data were in accordance to literature values.



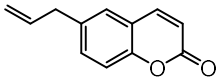
4-allylphenol: Prepared according to literature procedure



tert-butyl 5-allyl-1H-indole-1-carboxylate: Prepared according to literature procedure



5-allylbenzo[*b*]thiophene: Prepared according to literature procedure

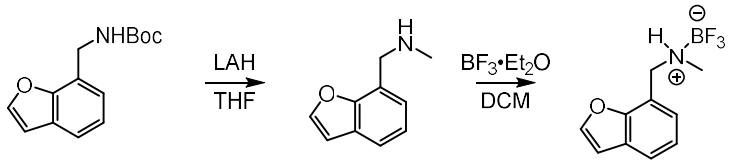


6-allyl-2*H*-chromen-2-one: Prepared according to literature procedure

***N*-methyl-1-(napthalen-1-yl)methanamine-borontrifluoride:** Following the general BF_3 complexation procedure, to a solution of *N*-methyl-1-(napthalen-1-yl)methanamine (0.82 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1 eq). Purification by column chromatography (SiO_2, 20% → 30% → 40% → 50% EtOAc/Hx) afforded *N*-methyl-1-(napthalen-1-yl)methanamine-borontrifluoride as a white solid (992 mg, 4.14 mmol, 83% yield). ^{1}H NMR (500 MHz, DMSO-

d$_6$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 8.00 (app. dd, *J* = 8.4, 2.9 Hz, 2H), 7.70 – 7.63 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.02 (br s, 1H), 4.71 (d, *J* = 14.0 Hz, 1H), 3.99 (dd, *J* = 14.1, 9.7 Hz, 1H), 2.30 – 2.27 (m, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 133.44, 131.71, 130.05, 129.45, 128.73, 128.70, 126.81, 126.11, 125.24, 123.48, 48.94, 32.91. ^{19}F NMR (471 MHz, DMSO-*d*$_6$) δ (-154.83) – (-154.62) (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_{12}H_{13}BF_3N$ [M—H]$^-$: 238.112; found 238.102.

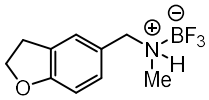
Scheme 2.7: Synthesis of 1-(benzofuran-7-yl)-N-methylmethanamine-borontrifluoride



Synthesis of 1-(benzofuran-7-yl)-N-*methylmethanamine:* To a flame-dried round-bottom flask was added lithium aluminum hydride (805 mg, 21.2 mmol, 4.0 eq) and dry THF (8 mL). The flask was cooled to 0 ºC, and to it was added dropwise a solution of *t*-butyl (benzofuran-7-ylmethyl)carbamate[1] (1.3 g, 5.30 mmol, 1 eq) in dry THF (8 mL). The vial containing the solution of *t*-butyl (benzofuran-7-ylmethyl)carbamate was rinsed once more with dry THF (2 mL) and added to the suspension of lithium aluminum hydride. An oven-dried reflux condenser was attached to the flask, and the solution was then refluxed under an argon atmosphere for 24 hours. The mixture was cooled to 0 ºC and H_2O (0.9 mL), 15% aqueous NaOH (0.9 ml), and H_2O (2.7 mL) were added sequentially. The slurry was stirred at room temperature for 15 minutes, and then to it was added a scoop of anhydrous Na_2SO_4. The slurry was stirred for an additional 15 minutes, and then filtered through celite and washed with 300 mL of EtOAc. The solvent was removed under reduced pressure to result in an orange oil (856 mg, 5.30 mmol, >99% yield) which was

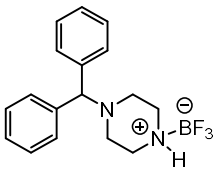
used directly without further purification. The crude ^{1}H NMR matched the reported spectra for 1-(benzofuran-7-yl)-*N*-methylmethanamine.

Synthesis of 1-(benzofuran-7-yl)-N-*methylmethanamine-borontrifluoride:* Following the general BF_3 complexation protocol, to a solution of 1-(benzofuran-7-yl)-*N*-methylmethanamine (850 mg, 5.30 mmol, 1.0 eq) in DCM (21 mL, 0.25M) was added BF_3•OEt_2 (0.73 mL, 5.83 mmol, 1.1 eq). Purification by column chromatography (SiO_2, 30% → 60% → 80% EtOAc/Hx) afforded 1-(benzofuran-7-yl)-N-methylmethanamine-borontrifluoride as a white solid (835 mg, 3.65 mmol, 69% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.23 (br s, 1H), 7.02 (d, J = 2.2 Hz, 1H), 4.39 (d, J = 13.9 Hz, 1H), 3.93 (dd, J = 13.8, 9.7 Hz, 1H), 2.25 – 2.22 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 153.44, 146.28, 127.37, 126.54, 122.96, 121.99, 116.43, 107.05, 45.87, 32.46. ^{19}F NMR (471 MHz, DMSO-d_6) δ (-154.69) – (-154.90) (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{11}BF_3NO$ $[M—H]^-$: 228.092; found 228.080.



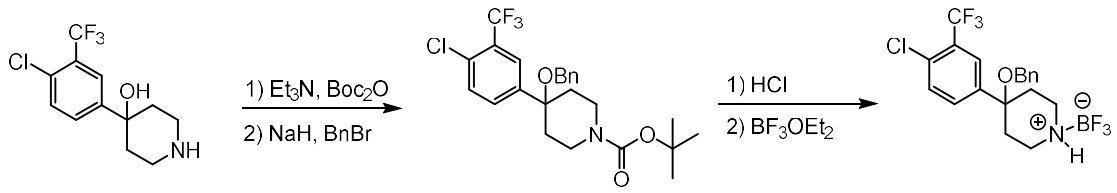
1-(2,3-dihydrobenzofuran-5-yl)-*N*-methylmethanamine-borontrifluoride: Following the general BF_3 complexation procedure 1-(2,3-dihydrobenzofuran-5-yl)-*N*-methylmethanamine (816 mg, 5 mmol, 1 eq) in DCM (20 mL, 0.25 M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded 1-(2,3-dihydrobenzofuran-5-yl)-N-methylmethanamine-borontrifluoride as a white solid (617 mg, 2.66 mmol, 53% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (s, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.62 (t, J = 8.7 Hz, 2H), 4.41 (d, J = 13.7 Hz, 1H), 3.82 (br s, 1H), 3.50 (dd, J = 13.7, 10.4 Hz, 1H), 3.24 (t, J = 8.7 Hz, 2H), 2.46 (d, J = 5.4 Hz, 3H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 161.19, 130.05, 128.75, 126.40, 124.29, 110.07, 71.77, 53.49, 32.69, 29.62. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.17 (q, *J* = 15.5 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{10}H_{12}NOF_3B$ [M—H]$^-$: 230.0964; found 230.0960.



1-benzhydrylpiperazine-borontrifluoride: Following the general BF_3 complexation procedure to a solution of 1-benzhydrylpiperazine (1.26 g, 5 mmol, 1 eq) in DCM (20 mL, 0.25 M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1 eq). Purification by column chromatography (SiO_2, 20→60% EtOAc/Hexanes) afforded 1-benzhydrylpiperazine-borontrifluoride as a white solid (1.11 g, 3.47 mmol, 69%) ^1H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.4 Hz, 4H), 7.30 (t, *J* = 7.6 Hz, 4H), 7.21 (t, *J* = 7.5 Hz, 2H), 4.28 (s, 1H), 3.56 (br s, 1H), 3.22 (d, *J* = 10.9 Hz, 2H), 3.13 – 2.96 (m, 4H), 2.08 (t, *J* = 11.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.42, 128.99, 127.83, 127.66, 75.84, 50.58, 45.47. ^{19}F NMR (471 MHz, Chloroform-*d*) δ (-157.29) – (-157.63) (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_{17}H_{19}N_2BF_3$ [M—H]$^-$: 319.1588; found 319.1591.

Scheme 2.8: Synthesis of 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-borontrifluoride

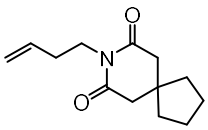


Synthesis of tert-*butyl 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-1-carboxylate*: An oven dried flask was charged with 4-(4-chloro-3-(trifluoromethyl)phenyl)piperidin-4-ol (2.24g, 8 mmol, 1 eq). Under nitrogen, DCM was added

(70 mL, 0.11 M), and the solution was cooled to 0 °C. Et_3N (2.8 mL, 20 mmol, 2.5 eq) was added. While stirring at 0 °C, Boc_2O was added slowly (1.92 g, 8.8 mmol, 1 eq). The solution was allowed to warm to room temperature and stirred overnight. Afterwards, the solution was quenched with H_2O. The organic phase was extracted three times with DCM and dried over $MgSO_4$. Concentration under reduced pressure afforded *tert*-butyl 4-(4-chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidine-1-carboxylate. The crude product was used without any further purification. An oven dried flask was charged with the crude *tert*-butyl 4-(4-chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidine-1-carboxylate. DMF (24 mL) was added under nitrogen. The solution was cooled to 0 °C. NaH (211 mg, 8.8 mmol, 1.1 eq) was added slowly. The solution was stirred at 0 °C for 20 minutes. Benzyl bromide (xx mL, xx mmol, xx eq). was then added slowly. The solution was allowed to warm to room temperature and stirred overnight. The crude mixture was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was extracted with EtOAc (3 x) and washed once with brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 5% → 10% →15% EtOAc/Hx) afforded *tert*-butyl 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-1-carboxylate as a clear oil (3.53 g, 7.5 mmol, 94% yield over two steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 2H), 7.21 – 7.15 (m, 3H), 4.00 (s, 2H), 3.95 (app br s, 2H) 3.16 (app br s, 2H), 2.02 (app br s, 2H), 1.79 (app br s, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.84, 144.03, 137.91, 131.77, 131.47, 130.54, 128.52 (q, *J* = 31.4 Hz), 128.50, 127.70, 127.43, 125.20 (q, *J* = 5.3 Hz), 122.85 (q, *J* = 274.2 Hz), 79.69, 75.69, 64.47, 39.89, 39.07, 35.49, 34.45, 28.47. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.41. HRMS (ESI) m/z calc'd for $C_{24}H_{28}NO_3ClF_3$ $[M+H]^+$: 470.1710; found 470.1697.

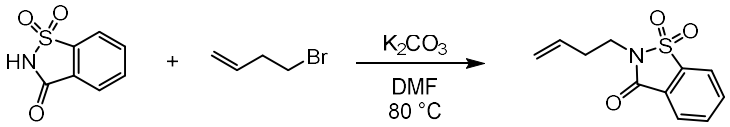
Synthesis of 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-borontrifluoride: A flask was charged with *tert*-butyl 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-1-carboxylate (3.43g, 7.3 mmol, 1 eq), dioxane (5 mL, 1.5 M) and 4M HCl in dioxane (5 mL, 20 mmol, 2.74 eq). The mixture was allowed to stir overnight, forming a white precipitate. The crude mixture was concentrated under reduced pressure and mixed with Et_2O to precipitate the amine hydrochloride salt. The salt was filtered and triturated with Et_2O. The precipitate was dissolved in DCM and basified with a saturated K_2CO_3 in H_2O to a pH of 14. The layers were seperated and the aqueous layer was extracted with DCM two times. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine (2.45g, 6.6 mmol, 91% yield). The crude 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine was used directly in the next step with no other purification. Following the general BF_3 complexation procedure to a solution of 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine (1.85 g, 5 mmol, 1 eq) in DCM (20 mL, 0.25 M) was added BF_3•OEt_2 (0.68 mL, 5.5 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded 4-(benzyloxy)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-borontrifluoride as a white solid (1.55 g, 3.54 mmol, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.57 (app s, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.32 (app t, *J* = 7.1 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 4.10 (s, 2H), 3.76 (br s, 1H), 3.46 – 3.27 (m, 4H), 2.39 (d, *J* = 14.5 Hz, 2H), 2.03 (td, *J* = 13.9, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.26, 137.14, 132.46, 132.27, 130.41, 129.08 (q, *J* = 31.5 Hz), 128.80, 128.19, 127.57, 125.17 (q, *J* = 5.3 Hz), 121.81 (q, *J* = 273.8 Hz), 74.07, 65.01, 41.43, 33.70. ^{19}F NMR (471 MHz, Chloroform-

d) δ -62.52, (-156.97) – (-157.21) (m). HRMS (ESI-TOF EI–) m/z calc'd for $C_{19}H_{18}NOClF_6B$ $[M—H]^-$: 436.1074; found 436.1073.



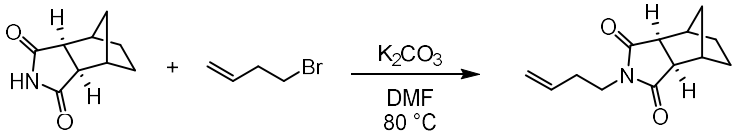
8-(but-3-en-1-yl)-8-azaspiro[4.5]decane-7,9-dione: Prepared according to literature procedure. Spectral data was in accordance to literature values.

Scheme 2.9: Synthesis of 2-(but-3-en-1-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide

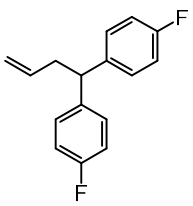


An oven dried flask was charged with saccharin (916 mg, 5 mmol, 1 eq), and K_2CO_3 (830 mg, 6 mmol, 1.2 eq). DMF (10 mL, 0.5 M) was added under nitrogen, followed by 4-bromo-1-butene. The solution was stirred at 80 °C for 23 hours. The crude mixture was then quenched with H_2O and diluted with EtOAc. After the layers were separated, the organic layer was washed two times with H_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 10→30% EtOAc/Hx) afforded 2-(but-3-en-1-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide as a green solid (763 mg, 3.17 mmol, 64% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 5.84 (ddt, *J* = 17.0, 9.9, 6.9 Hz, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 2.61 (app q, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.98, 137.79, 134.83, 134.44, 133.85, 127.51, 125.30, 121.05, 118.19, 38.76, 32.84. HRMS (ESI) m/z calc'd for $C_{11}H_{12}NO_3S$ $[M+H]^+$: 238.0538; found 238.0529.

Scheme 2.10: Synthesis of (3aR,4S,7R,7aS)-2-(but-3-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione

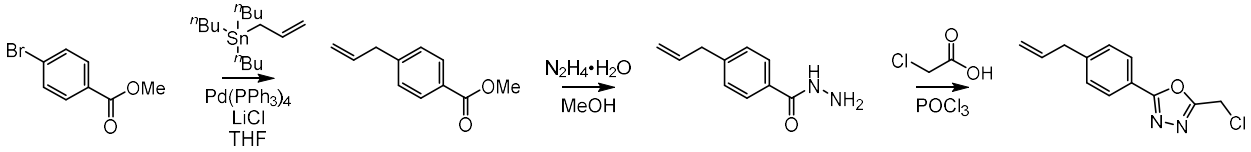


To an oven-dried flask was added K_2CO_3 (830 mg, 6 mmol, 1.2 eq), DMF (10 mL, 0.5 M), (3aR,4S,7R,7aS)-hexahydro-1H-4,7-methanoisoindole-1,3(2*H*)-dione (826 mg, 5 mmol, 1.0 eq), and 4-bromo-1-butene (0.56 mL, 5.5 mmol, 1.1 eq). The solution was heated to 80 ºC and stirred for 17 hours under argon. The mixture was diluted with H_2O and EtOAc, the layers were separated, and then the organic layer was washed with H_2O (2x). The organic layer was dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 30% EtOAc/Hx) afforded (3aR,4S,7R,7aS)-2-(but-3-en-1-yl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione as a clear oil at room temperature and white solid at -30 ºC (1.1 g, 5 mmol, >99% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.71 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.54 (t, *J* = 7.1 Hz, 2H), 2.67 (br s, 2H), 2.57 (s, 2H), 2.32 (app q, *J* = 7.1 Hz, 2H), 1.67 – 1.62 (m, 2H), 1.34 – 1.29 (m, 2H), 1.20 – 1.11 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.06, 134.67, 117.61, 48.72, 39.77, 38.07, 33.17, 32.17, 28.18. HRMS (ESI-TOF ES$^+$) m/z calc'd for $C_{13}H_{17}NO_2$ $[M+H]^+$: 220.1293; found 220.1341.



4,4'-(but-3-ene-1,1-diyl)bis(fluorobenzene): Prepared according to literature procedure. Spectral data were in accordance to literature values

Scheme 2.11: Synthesis of 2-(4-allylphenyl)-5-(chloromethyl)-1,3,4-oxadiazole



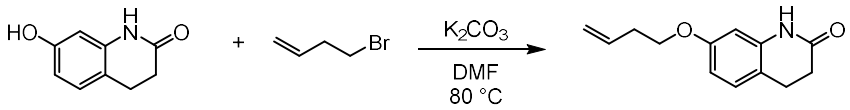
Synthesis of methyl-4-allylbenzoate: In a glovebox to a flame-dried round-bottom flask and stir bar was added anhydrous LiCl (4.2 g, 100 mmol, 5 eq). The flask was removed from the glovebox, and to it was added methyl-4-bromobenzoate (4.3 g, 20 mmol, 1 eq). The flask was placed under vacuum and then purged with N_2 (3x). To the flask was added THF (200 mL, 0.1 M) and allyltributylstannane (6.8 mL, 22 mmol, 1.1 eq), and then the solution was stirred and sparged with argon for 15 minutes. The flask was charged with $Pd(PPh_3)_4$ (2.3 g, 2 mmol, 0.1 eq), topped with an oven-dried reflux condenser, and stirred for 22 hours at 80 ºC under argon. The solution was then cooled to room temperature and quenched with a aqueous solution of 9.3% (v/v) NH_4OH (100 mL). The aqueous layer was washed with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under a stream of nitrogen to result in a yellow oil. Purification *via* column chromatography (SiO_2, 0% → 1% → 2% → 4% Et_2O/pentane) followed by a second column chromatography (SiO_2, 1% → 1.5% → 2% → 3% Et_2O/Hx) afforded methyl-4-allylbenzoate as a clear oil at room temperature and white solid at -30 ºC (1.7 g, 9.7 mmol, 49% yield). Spectral data were in accordance to literature values.

Synthesis of 4-allylbenzohydrazide: To a round-bottom flask was added 4-methyl-allylbenzoate (1.7 g, 9.7 mmol, 1 eq), MeOH (20 mL, 0.5 M), and $N_2H_4 \cdot H_2O$ (4.9 mL, 97.2 mmol, 10 eq). The flask was topped with a reflux condenser and the mixture was refluxed for 24 hours open to air. The mixture was cooled to room temperature, methanol was removed under reduced pressure, and then the residue was diluted with DCM (100 mL) and H_2O (50 mL). The formed layers were

separated, and the aqueous layer was washed with DCM (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. The resulting solid was recrystallized from hot toluene and then washed with cold toluene to afford 4-allylbenzohydrazide as a white crystalline solid (1.1 g, 6.2 mmol, 62% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (br s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.94 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.12 – 5.04 (m, 2H), 4.11 (br s, 2H), 3.42 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.73, 144.48, 136.53, 130.59, 129.04, 127.16, 116.70, 40.11. HRMS (ESI – TOF ES+) m/z calc'd for $C_{10}H_{12}N_2O$ $[M+H]^+$: 177.0983; found 177.1027.

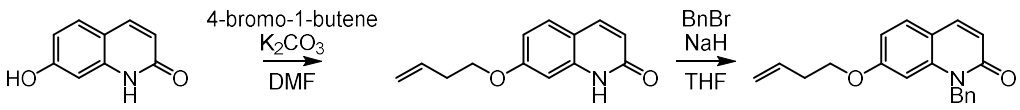
Synthesis of 2-(4-allylphenyl)-5-(chloromethyl)-1,3,4-oxadiazole: To a flame-dried round-bottom flask was 4-allylbenzohydrazide (528 mg, 3 mmol, 1 eq), chloroacetic acid (284 mg, 3 mmol, 1 eq), and freshly-distilled $POCl_3$ (2.1 mL, 22.5 mmol, 7.5 eq). The flask was topped with an oven-dried reflux condenser and stirred at 80 ºC under argon for 8 hours. *(Note: Using freshly distilled $POCl_3$ and keeping the temperature at or below 80 ºC was critical to preventing the formation of inseparable olefin isomers*). The mixture was cooled to 0 ºC and Sat. $NaHCO_3$ (100 mL) was added slowly to quench the mixture until a pH of 8 was achieved. The resulting slurry was filtered, washed with large volumes of cold water, and then allowed to dry on the funnel. Purification *via* column chromatography (SiO_2, 5% → 7.5% → 10% EtOAc/Hx.) afforded 2-(4-allylphenyl)-5-(chloromethyl)-1,3,4-oxadiazole as a white solid (314 mg, 1.3 mmol, 45% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.97 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H), 5.17 – 5.08 (m, 2H), 4.77 (s, 2H), 3.47 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.22, 162.08, 144.98, 136.32, 129.55, 127.38, 121.33, 116.97, 40.26, 33.18. HRMS (ESI-TOF ES+) m/z calc'd for $C_{12}H_{11}ClN_2O$ $[M+H]^+$: 235.0593; found 235.0628.

Scheme 2.12: Synthesis of 7-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1*H*)-one



To a flame-dried round bottom flask was added K_2CO_3 (2.8 g, 20 mmol, 2 eq), 7-hydroxy-3,4-dihydrocarbostyril (1.6 g, 10 mmol, 1 eq), dry DMF (50 mL, 0.2 M), and 4-bromo-1-butene (1.5 mL, 15 mmol, 1.5 eq). The suspension was heated to 80 ºC and stirred under argon for 24 hours. The mixture was cooled to room temperature and diluted with EtOAc (100 mL) and H_2O (100 mL), then separated. The aqueous layer was washed with EtOAc (2 x 50 mL), and then the combined organic layers were washed with H_2O (5 x 50 mL) and brine (1 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 20% → 25% → 30% → 35% EtOAc/Hx eluent) afforded 7-(but-3-en-1-yloxy)-3,4-dihydroquinolin-2(1H)-one as a white solid (961 mg, 4.4 mmol, 44% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.79 (br s, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.89 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.16 (app dd, *J* = 17.2, 1.7 Hz, 1H), 5.10 (app dd, *J* = 10.3, 1.4 Hz, 1H), 3.98 (t, *J* = 6.7 Hz, 2H), 2.89 (app t, *J* = 8.5 2H), 2.61 (app t, *J* = 8.5 2H), 2.52 (app qt, *J* = 6.6, 1.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.31, 158.67, 138.34, 134.49, 128.71, 117.21, 115.93, 108.88, 102.52, 67.54, 33.73, 31.19, 24.70. HRMS (ESI-TOF ES+) m/z calc'd for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.1136; found 218.1183.

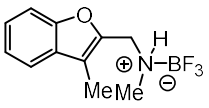
Scheme 2.13: Synthesis of 1-benzyl-7-(but-3-en-1-yloxy)quinolin-2(1*H*)-one



Synthesis of 7-(but-3-en-1-yloxy)quinolin-2(1H)-one: To a flame-dried round bottom flask was added K_2CO_3 (5.5 g, 40 mmol, 4 eq), 7-hydroxyquinolin-2(1H)-one (1.6 g, 10 mmol, 1 eq), anhydrous DMF (50 mL, 0.2 M), and 4-bromo-1-butene (3.1 mL, 30 mmol, 3 eq). The suspension was heated to 80 ºC and stirred under argon for 24 hours. The mixture was cooled to room temperature and diluted with EtOAc (100 mL) and H_2O (100 mL), then separated. The aqueous layer was washed with EtOAc (2 x 50 mL), and then the combined organic layers were washed with H_2O (5 x 100 mL) and brine (1 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. The crude product was recrystallized from hot MeOH, washed with cold methanol, and volatiles were removed under reduced pressure to afford 7-(but-3-en-1-yloxy)quinolin-2(1*H*)-one as a yellow crystalline solid (985 mg, 4.6 mmol, 46% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.55 (br s, 1H), 7.73 (d, *J* = 9.4 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.56 (d, *J* = 9.4 Hz, 1H), 5.92 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.13 (d, *J* = 10.3 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 2.57 (app q, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.25, 161.39, 140.96, 140.55, 134.31, 129.13, 118.12, 117.46, 114.39, 112.75, 99.25, 67.74, 33.65. HRMS (ESI-TOF ES+) m/z calc'd for $C_{13}H_{13}NO_2$ $[M+H]^+$: 216.0980; found 216.1024.

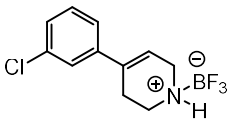
Synthesis of 1-benzyl-7-(but-3-en-1-yloxy)quinolin-2(1H)-one: To a flame-dried round-bottom flask was added 7-(but-3-en-1-yloxy)quinolin-2(1H)-one (428 mg, 2 mmol, 1 eq) and anhydrous DMF (4 mL, 0.5 M). The flask was cooled to 0 ºC and to it was added 95% NaH (72 mg, 3 mmol, 1.5 eq). The suspension was stirred at room temperature for 15 minutes. To the flask was added benzyl bromide (0.36 mL, 3 mmol, 1.5 eq), and then the mixture was heated to 60 ºC and stirred

for 17 hours under argon. The mixture was cooled to room temperature and quenched with H_2O (10 mL) and then diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was washed with EtOAc (2 x 20 mL). The combined organic layers were washed with H_2O (5 x 50 mL) and brine (1 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 20% → 25% → 30% EtOAc/Hx eluent) afforded 1-benzyl-7-(but-3-en-1-yloxy)quinolin-2(1*H*)-one as a white solid (445 mg, 1.5 mmol, 73% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 9.4 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.21 (m, 3H), 6.76 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.64 (d, *J* = 9.4 Hz, 1H), 5.84 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.52 (br s, 2H), 5.17 – 5.04 (m, 2H), 3.93 (t, *J* = 6.7 Hz, 2H), 2.47 (app qt, *J* = 6.7, 1.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.05, 161.11, 141.26, 139.45, 136.56, 134.04, 130.19, 128.95, 127.41, 126.79, 118.54, 117.46, 115.23, 110.71, 100.19, 67.52, 46.19, 33.41. HRMS (ESI-TOF ES+) m/z calc'd for $C_{20}H_{19}NO_2$ $[M+H]^+$: 306.1449; found 306.1488.



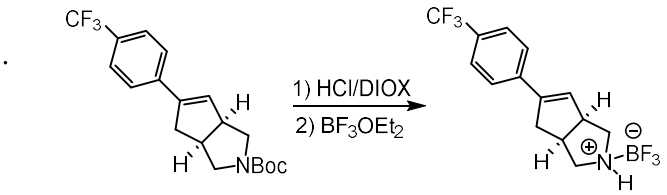
_N_-methyl-1-(3-methylbenzofuran-2-yl)methanamine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of *N*-methyl-1-(3-methylbenzofuran-2-yl)methanamine (505 mg, 2.88 mmol, 1 eq) in THF (12 mL, 0.24M) was added BF_3•OEt_2 (0.39 mL, 3.17 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded *N*-methyl-1-(3-methylbenzofuran-2-yl)methanamine-borontrifluoride as a white solid (561 mg, 2.31 mmol, 80% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.48 (br s, 1H), 7.36 (app t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 4.20 (d, *J* = 14.9 Hz, 1H), 3.89 (dd, *J* = 14.9, 8.5 Hz, 1H), 2.36 (br s, 3H), 2.25 (s, 3H). ^{13}C NMR (126

MHz, DMSO) δ 153.73, 145.46, 128.94, 125.10, 122.67, 120.01, 116.41, 111.02, 42.97, 33.10, 7.71. ^{19}F NMR (471 MHz, DMSO-d_6) δ -154.69 (q, J = 17.9, 17.4 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{11}H_{12}BNOF_3$ [M—H]$^-$: 242.0964; found 242.0961.



4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridine (581 mg, 3 mmol, 1 eq) in THF (12 mL, 0.25M) was added BF_3•OEt_2 (0.41 mL, 3.3 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded 4-(3-chlorophenyl)-1,2,3,6-tetrahydropyridine-borontrifluoride as a white solid (587 mg, 2.24mmol, 75% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (s, 1H), 7.32 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 6.10 (app br s, 1H), 4.05 (br s, 1H), 3.81 (app d, J = 18.0 Hz, 1H), 3.74 – 3.63 (m, 2H), 3.04 (qd, J = 12.2, 4.9 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.65 (app d, J = 18.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.77, 134.84, 134.65, 130.06, 128.38, 125.43, 123.29, 119.03, 44.28, 42.64, 25.52. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.50 (q, J = 14.6 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{11}H_{11}BNF_3Cl$ [M—H]$^-$: 260.0625; found 260.0627.

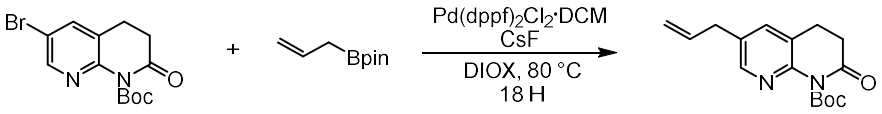
Scheme 2.14: Synthesis of 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole-borontrifluoride:



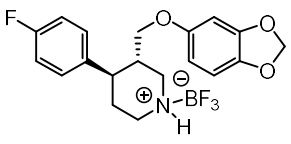
A flask was charged with *tert*-butyl 5-(4-(trifluoromethyl)phenyl)-3,3a,4,6a-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (2.12 g, 6 mmol, 1 eq), dioxane (4.1 mL, 1.5

M) and 4M HCl in dioxane (4.1 mL, 20 mmol, 2.75 eq). The mixture was allowed to stir overnight, forming a white precipitate. The crude mixture was concentrated under reduced pressure and mixed with Et_2O to precipitate the amine hydrochloride salt. The salt was filtered and triturated with Et_2O. The precipitate was dissolved in DCM and basified with a saturated K_2CO_3 in H_2O to a pH of 14. The layers were seperated and the aqueous layer was extracted with DCM two times. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to afford 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole (1.11 g, 4.6 mmol, 73% yield). The crude 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole was used directly in the next step with no other purification. Following the general BF_3 complexation procedure to a solution of 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole (760 mg, 3 mmol, 1 eq) in THF (12 mL, 0.25 M) was added BF_3•OEt_2 (0.41 mL, 3.3 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded 5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole - borontrifluoride as a white solid (769 mg, 2.40 mmol, 80% yield, 3:1 *d.r.*). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 6.14 (s, 0.24H), 6.01 (s, 0.76H), 4.53 (br s, 0.26H), 4.41 (br s, 0.75H), 3.83 – 3.77 (m, 0.77H), 3.72 – 3.55 (m, 0.75H), 3.38 – 3.08 (m, 4.86H), 3.06 – 2.91 (m, 0.51H), 2.80 – 2.58 (m, 1.26H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.55, 140.85, 138.65, 138.08, 130.17 (q, J = 32.5 Hz), 129.94 (q, J = 32.8 Hz), 127.86, 127.13, 126.42, 126.29, 125.63 (q, J = 3.9 Hz), 124.22 (q, J = 272.7 Hz), 124.18 (q, J = 271.5 Hz) 55.89, 53.03, 52.04, 50.71, 50.02, 41.33, 40.98, 38.58, 36.38. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.49, -62.52, -155.51 (q, J = 15.1 Hz), -155.86 (q, J = 15.2 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{14}H_{13}NF_6B$ $[M—H]^-$: 320.1045; found 320.1050.

Scheme 2.15: Synthesis of *tert*-butyl 6-allyl-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxylate

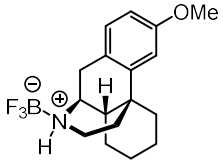


An oven dried round-bottom flask was charged with *tert*-butyl 6-bromo-2-oxo-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxylate (652 mg, 2 mmol, 1 eq) and CsF (1.45 g, 9.54 mmol, 4.77 eq). Dioxane (30 mL, 0.067 M) was added under nitrogen. The solution was sparged with argon for 5 minutes. Afterwards, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.75 mL, 4 mmol, 2 eq) and Pd(dppf)Cl_2·DCM (196 mg, 0.24 mmol, 0.12 eq) were added. The solution was stirred at 80 °C for 18 hours. The crude mixture was cooled to room temperature, quenched with H_2O, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc two times. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude mixture was filtered and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 5% → 20% → 25% EtOAc/Tol.) afforded *tert*-butyl 6-allyl-2-oxo-3,4-dihydroquinoline-1(2H)-carboxylate as a yellow-white solid (463 mg, 1.61 mmol, 80% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (br s, 1H), 7.30 (br s, 1H), 5.90 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.32 (d, *J* = 6.5 Hz, 2H), 2.92 (app t, *J* = 7.3 Hz, 2H), 2.69 (dd, *J* = 8.5, 6.5 Hz, 2H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.62, 150.93, 149.08, 146.61, 136.50, 136.37, 131.10, 118.90, 116.87, 85.26, 36.66, 31.19, 27.81, 23.88. HRMS (ESI) m/z calc'd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$: 289.1552; found 288.1540.



(3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-borontrifluoride: Following the general BF_3

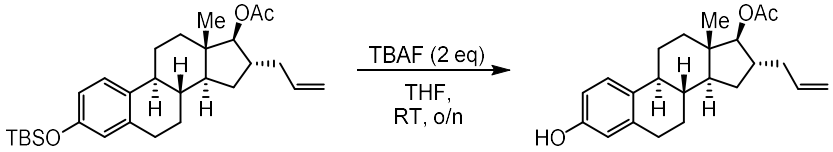
complexation procedure, to a solution of (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine (833 mg, 2.5 mmol, 1 eq) in DCM (10 mL, 0.25M) was added BF_3•OEt_2 (0.34 mL, 2.75 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-borontrifluoride as a white solid (789 mg, 1.99 mmol, 79% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 2H), 7.01 (app t, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.89 (s, 2H), 4.28 – 4.02 (m, 1H), 3.68 (app d, *J* = 14.1 Hz, 1H), 3.61 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.57 (app d, *J* = 12.8 Hz, 1H), 3.50 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.01 (q, *J* = 12.4 Hz, 1H), 2.94 (d, *J* = 12.4 Hz, 1H), 2.87 (td, *J* = 12.0, 3.9 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.15 – 2.07 (m, 1H), 1.99 – 1.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.03 (d, *J* = 245.8 Hz), 153.88, 148.37, 142.16, 137.38 (d, *J* = 3.3 Hz), 128.89 (d, *J* = 8.1 Hz), 116.01 (d, *J* = 21.3 Hz), 108.02, 105.71, 101.34, 98.10, 67.93, 48.55, 45.96, 42.16, 41.44, 32.33. ^{19}F NMR (471 MHz, Chloroform-*d*) δ (-114.71) – (-114.88) (m), -156.90 (q, *J* = 14.1 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{19}H_{19}BNO_3F_4Cl$ $[M—H]^-$: 396.1394; found 396.1406. $[\alpha]^{20}_D$ = -89.78 (c = 1.00, $CHCl_3$).



(4b*S*,8a*S*,9*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epiminoethano)phenanthrene-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of (4b*S*,8a*S*,9*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epiminoethano)phenanthrene (979 mg, 3.8 mmol, 1 eq) in THF (15.2 mL, 0.25M) was added BF_3•OEt_2 (0.52 mL, 4.18 mmol, 1.1 eq). Purification by column chromatography (SiO_2, DCM) afforded (4b*S*,8a*S*,9*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epiminoethano)phenanthrene-borontrifluoride as a white solid (823 mg, 2.53 mmol, 67%

yield, 17.7:1 d.r.). Diastereomeric ratio was determined by ^{19}F NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.76 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.01 (br s, 1H), 3.80 (s, 3H), 3.68 – 3.60 (m, 1H), 3.34 (d, *J* = 19.1 Hz, 1H), 3.08 – 3.01 (m, 1H), 3.01 (dd, *J* = 19.1, 6.2 Hz, 1H), 2.75 (qd, *J* = 13.3, 3.6 Hz, 1H), 2.40 (app d, *J* = 13.1 Hz, 1H), 1.77 – 1.65 (m, 3H), 1.64 – 1.53 (m, 2H), 1.49 (app d, *J* = 13.3 Hz, 1H), 1.44 – 1.28 (m, 3H), 1.12 (qd, *J* = 12.5, 3.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.90, 139.35, 129.36, 127.17, 111.78, 111.29, 55.42, 52.93, 45.08, 41.08, 39.39, 37.11, 36.00, 26.16, 26.04, 25.88, 21.82. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -150.13 (q, *J* = 16.8 Hz), -151.95 (q, *J* = 16.7 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_{17}H_{22}NOF_3B$ $[M—H]^-$: 324.1747; found 324.1750.

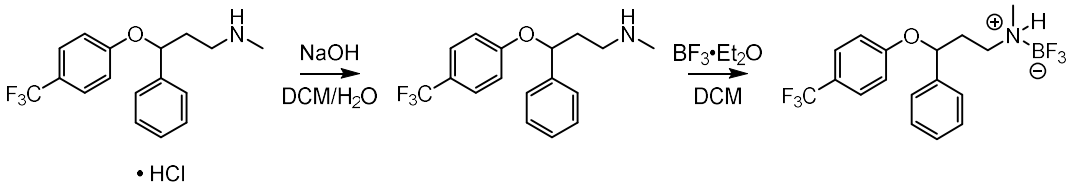
Scheme 2.16: Synthesis of (8*R*,9*S*,13*S*,14*S*,16*R*,17*S*)-16-allyl-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate



An oven dried round-bottom flask was charged with (8*R*,9*S*,13*S*,14*S*,16*R*,17*S*)-16-allyl-3-((tert-butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (1.21 g, 2.58 mmol, 1 eq). THF (5.2 mL, 0.5 M) was added under nitrogen, followed by TBAF (1M in THF, 5.2 mL, 2 eq). The solution was stirred at room temperature overnight. Afterwards, the mixture was concentrated under reduced pressure and purified *via* column chromatography (SiO_2, 5% → 10% → 20% → 30% EtOAc/Hx) to afford (8*R*,9*S*,13*S*,14*S*,16*R*,17*S*)-16-allyl-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate as a white solid (915 mg, 2.58 mmol, >99% yield). ^{1}H

NMR (500 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 8.4 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 5.77 (ddt, *J* = 16.4, 9.9, 6.4 Hz, 1H), 5.05 (d, *J* = 17.1 Hz, 1H), 4.99 (d, *J* = 9.9 Hz, 1H), 4.94 (s, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.32 – 2.21 (m, 2H), 2.21 – 2.09 (m, 3H), 2.07 (s, 3H), 1.90 – 1.82 (m, 1H), 1.80 – 1.74 (m, 1H), 1.69 – 1.57 (m, 1H), 1.53 – 1.29 (m, 6H), 0.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.45, 153.54, 138.27, 137.07, 132.63, 126.64, 115.91, 115.36, 112.83, 86.99, 48.55, 44.45, 43.88, 40.29, 39.13, 38.59, 37.09, 29.71, 29.53, 27.23, 26.26, 21.39, 12.89. HRMS (ASAP+) m/z calc'd for $C_{23}H_{30}O_3$ $[M]^+$: 354.2195; found 354.2184. $[\alpha]^{22}_D$ = -11.98 (c = 0.98, $CHCl_3$).

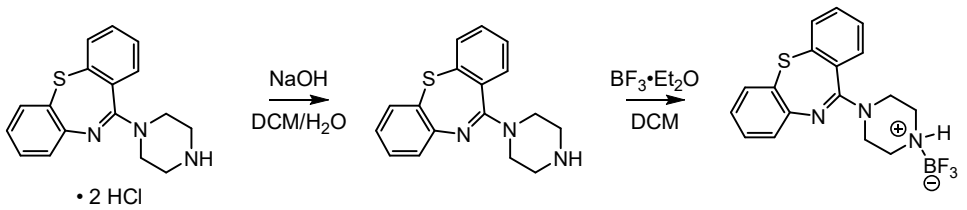
Scheme 2.17: Synthesis of 11-(piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine-borontrifluoride



Synthesis of N-methyl-3-phenoxy-3-phenylpropan-1-amine-borontrifluoride: To a separatory funnel was added *N*-methyl-3-phenoxy-3-phenylpropan-1-amine hydrochloride (780 mg, 2.25 mmol, 1 eq), DCM (30 mL), H_2O (15 mL) and 1 M NaOH (3.4 mL). The contents were mixed, layers were separated, and the aqueous layer was washed with DCM (3 x 30 mL). The combined organic layers were washed with H_2O (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure to afford *N*-methyl-3-phenoxy-3-phenylpropan-1-amine (690 mg, 2.25 mmol, >99% yield) as a yellow oil that was used without further purification. Following the general BF_3 complexation protocol, to a solution of *N*-methyl-3-phenoxy-3-phenylpropan-1-amine (690 mg, 2.25 mmol, 1 eq) in DCM (9 mL, 0.25M) was added BF_3•OEt_2 (310 μL, 2.5 mmol, 1.1 eq). Purification *via* plug (SiO_2, DCM) afforded *N*-

methyl-3-phenoxy-3-phenylpropan-1-amine-borontrifluoride as a colorless semi-solid (703 mg, 1.86 mmol, 83% yield) as a 1:1 mixture of diastereomers. The diastereomeric ratio was determined by ^{19}F NMR. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.42 – 7.35 (m, 2H), 7.35 – 7.28 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.41 – 5.32 (m, 1H), 4.37 (br s, 0.5H), 4.22 (br s, 0.5H), 3.54 – 3.50 (m, 0.5H), 3.50 – 3.39 (m, 0.5H), 2.85 (app sept, *J* = 7.0 Hz, 1H), 2.68 (d, *J* = 5.8 Hz, 1.5H), 2.64 (d, *J* = 5.8 Hz, 1.5H), 2.43 – 2.24 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.46, 159.27, 139.28, 138.76, 129.39, 128.80, 128.77, 127.17 (q, *J* = 3.8 Hz), 125.72, 125.58, 124.27 (q, *J* = 271.1 Hz), 124.26 (q, *J* = 32.8 Hz), 124.25 (q, *J* = 271.1 Hz), 124.02 (q, *J* = 32.8 Hz) 116.29, 115.87, 80.51, 79.57, 48.29, 47.84, 35.06 (d, *J* = 2.4 Hz), 34.51 (d, *J* = 2.3 Hz), 34.14, 33.91. *Note:* 24 of the expected 26 signals are present – two of the signals (129.39 and 127.17 ppm) account for both diastereomers. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.75, -61.79, -156.69 (q, *J* = 14.2 Hz), -157.10 (q, *J* = 15.1 Hz). HRMS (ESI – TOF ES-) m/z calc'd for $C_{17}H_{18}BF_6NO$ $[M—H]^-$: 376.1422; found 376.1302.

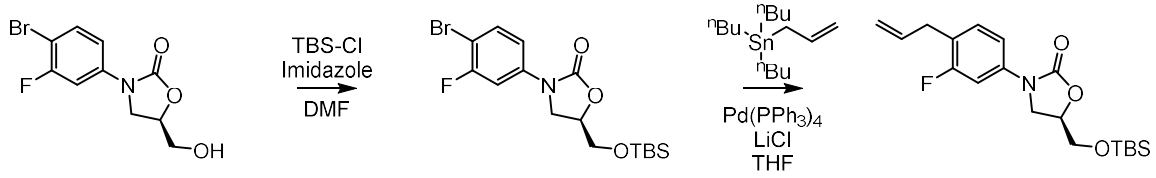
Scheme 2.18: Synthesis of 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine-borontrifluoride



Synthesis of 11-(piperazin-1-yl)dibenzo[b,f][1,4]thiazepine-borontrifluoride: To a separatory funnel was added 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine dihydrochloride (2 g, 5.5 mmol, 1 eq), DCM (50 mL), H_2O (20 mL) and 1 M NaOH (12 mL). The contents were mixed, layers were separated, and the aqueous layer was washed with DCM (3 x 30 mL). The combined organic layers were washed with H_2O (2 x 50 mL). The combined organic layers were dried over Na_2SO_4,

filtered, and volatiles were removed under reduced pressure to afford 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine (1.6 g, 5.5 mmol, >99% yield) as a yellow oil that was used without further purification. Following the general BF_3 complexation protocol, to a solution of 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine (1.6 g, 5.5 mmol, 1 eq) in DCM (21 mL, 0.25M) was added BF_3•OEt_2 (0.7 mL, 5.8 mmol, 1.1 eq). Purification *via* flash column chromatography (SiO_2, 20% → 30% → 40% → 50% → 70% EtOAc/Hx) afforded 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine-borontrifluoride as an off-white solid (1.7 g, 4.76 mmol, 87% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 (app d, *J* = 4.1 Hz, 2H), 7.21 (app td, *J* = 7.6, 1.5 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.96 (app td, *J* = 7.5, 1.5 Hz, 1H), 4.36 – 3.99 (m, 3H), 3.37 (app d, *J* = 13.2 Hz, 1H), 3.30 – 3.08 (m, 3H), 3.06 – 2.97 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.52, 148.07, 140.37, 133.42, 132.60, 132.48, 131.66, 129.42, 128.84, 128.11, 125.43, 124.04, 44.83, 44.56. *Note:* 13 of 14 carbon peaks accounted for. One set of carbon resonances (131.66 ppm) are equal to each other as indicated by the ^{1}H-^{13}C HSQC spectrum and accounts for the missing carbon signal. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -156.77 (q, *J* = 11.0 Hz). HRMS (ESI – TOF ES-) m/z calc'd for $C_{17}H_{17}BF_3N_3S$ [M—H]$^-$: 362.1225; found 362.1111.

Scheme 2.19: Synthesis of (*R*)-3-(4-allyl-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one

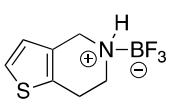


Synthesis of (R)-3-(4-bromo-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one: To a flame-dried round bottom flask was added (*R*)-3-(4-bromo-3-fluorophenyl)-5-

(hydroxymethyl)oxazolidin-2-one (2.9 g, 10 mmol, 1 eq), imidazole (1.4 g, 20 mmol, 2 eq), and DCM (30 mL, 0.3 M). The flask was cooled to 0 ºC and then TBS-Cl (2.26 g, 15 mmol, 1.5 eq) was added in one portion. The mixture was allowed to warm to room temperature and stirred overnight under an Argon atmosphere. To the mixture was added 1 M citric acid (30 mL). The layers were mixed and allowed to separate. The organic layer was washed with water (2 x 30 mL), and then the combined aqueous layers were washed with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure. Purification *via* flash column chromatography (SiO_2, 30% → 35% → 40% Et_2O/Hx eluent) afforded (*R*)-3-(4-bromo-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one as a white solid (4 g, 10 mmol, >99% yield) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (dd, *J* = 11.0, 2.6 Hz, 1H), 7.50 (t, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.73 – 4.65 (m, 1H), 4.00 (app t, *J* = 8.7 Hz, 1H), 3.95 – 3.88 (m, 2H), 3.78 (dd, *J* = 11.4, 3.1 Hz, 1H), 0.83 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.28 (d, *J* = 245.8 Hz), 154.43, 139.28 (d, *J* = 9.8 Hz), 133.53 (d, *J* = 1.7 Hz), 114.37 (d, *J* = 3.4 Hz), 106.65 (d, *J* = 27.9 Hz), 103.00 (d, *J* = 21.2 Hz), 72.60, 63.52, 46.57, 25.79, 18.26, -5.30, -5.35. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -105.02 (dd, *J* = 11.0, 7.7 Hz). HRMS (ESI) m/z calc'd for $C_{16}H_{23}BrFNO_3Si$ $[M+H]^+$: 404.0648; found 404.0692. $[\alpha]^{23}_D$ = -37.33 (c = 1.00, $CHCl_3$).

*Synthesis of (*R*)-3-(4-allyl-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one:* In a glovebox to a flame-dried round-bottom flask and stir bar was added anhydrous LiCl (787 mg, 18.6 mmol, 5 eq). The flask was removed from the glovebox, and to it was added (*R*)-3-(4-bromo-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one (1.5 g, 3.7 mmol, 1 eq). The flask was placed under vacuum and then purged with N_2 (3x). To the flask was

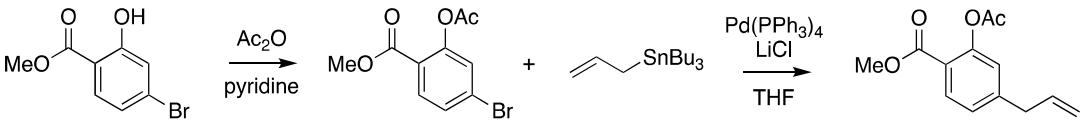
added argon-sparged THF (37 mL, 0.1 M) and allyltributylstannane (1.3 mL, 4.1 mmol, 1.1 eq). The flask was charged with $Pd(PPh_3)_4$ (440 mg, 0.37 mmol, 0.1 eq), topped with an oven-dried reflux condenser, and stirred for 22 hours at 80 ºC under argon. The solution was then cooled to room temperature and filtered through a plug of celite. The filtrate was washed with 1M NaOH (1 x 20 mL). The aqueous layer was washed with EtOAc (2 x 10 mL). The combined organic layers were washed successively with 1 M NaOH (1 x 20 mL), H_2O (2 x 30 mL), and brine (1 x 30 mL). The organic layer w dried over Na_2SO_4, filtered, and volatiles were removed under a stream of nitrogen to result in a black oil. Purification *via* column chromatography (SiO_2, 7.5% → 10% → 12.5% → 15% Et_2O/Hx) followed by a second column chromatography (SiO_2, 10% → 12.5% → 15% → 20% → 25% Et_2O/Hx) afforded (*R*)-3-(4-allyl-3-fluorophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)oxazolidin-2-one as a white solid (839 mg, 2.3 mmol, 62% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 12.1, 2.1 Hz, 1H), 7.21 – 7.12 (m, 2H), 5.94 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.71 – 4.63 (m, 1H), 4.00 (app t, *J* = 8.7 Hz, 1H), 3.95 – 3.86 (m, 2H), 3.79 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.37 (d, *J* = 6.4 Hz, 2H), 0.85 (s, 9H), 0.08 (s, 6H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.03 (d, *J* = 244.7 Hz), 154.66, 138.15 (d, *J* = 10.9 Hz), 135.90, 130.88 (d, *J* = 6.3 Hz), 122.26 (d, *J* = 16.5 Hz), 116.27, 113.38 (d, *J* = 3.3 Hz), 105.78 (d, *J* = 28.0 Hz), 72.55, 63.59, 46.79, 32.65 (d, *J* = 2.4 Hz), 25.83, 18.30, -5.27, -5.33. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -116.19 (dd, *J* = 12.0, 7.5 Hz). HRMS (ESI) m/z calc'd for $C_{19}H_{28}FNO_3Si$ $[M+H]^+$: 366.1856; found 366.1897. $[\alpha]^{24}_D$ = -35.42 (c = 1.01, $CHCl_3$).



4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-borontrifluoride: Following the general BF_3 complexation procedure, to a solution of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (0.61 mL, 5 mmol, 1 eq) in DCM (20 mL, 0.25 M) was added BF_3•OEt_2 (0.68 mL, 5.5

mmol, 1.1 eq). Purification by flash column chromatography (SiO_2, 30% → 50% EtOAc/Hx as an eluent) afforded 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-borontrifluoride as a white solid (831.4 mg, 4.02 mmol, 82% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 5.3 Hz, 1H), 6.81 (d, *J* = 5.2 Hz, 1H), 4.30 (dd, *J* = 15.9, 3.5 Hz, 1H), 4.09 (dd, *J* = 16.1, 10.9 Hz, 1H), 3.88 – 3.76 (m, 2H), 3.19 – 3.07 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 131.64, 129.40, 125.29, 124.94, 45.39, 43.84, 23.72. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -157.59 (q, *J* = 14.1 Hz). HRMS (ESI-TOF EI–) m/z calc'd for $C_7H_8BF_3NS$ $[M—H]^-$: 206.0423; found 206.0428.

Scheme 2.20: Synthesis of methyl 2-acetoxy-4-allylbenzoate



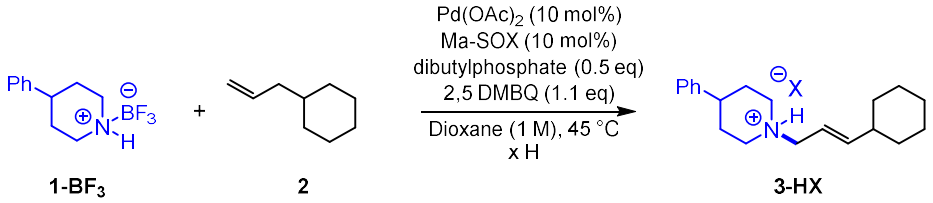
Synthesis of methyl 2-acetoxy-4-bromobenzoate: To a solution of methyl 4-bromo-2-hydroxybenzoate[12] (1.70 g, 7.36 mmol, 1 eq) in pyridine (15 mL, 0.5 M) was added acetic anhydride (2.78 mL, 29.43 mmol, 4 eq) dropwise. The reaction was allowed to stir at room temperature for 4.5 h, in which the reaction completion was monitored by TLC. The resulting solution was cooled to 0 °C, diluted with DCM (50 mL), and quenched with water (50 mL). The aqueous and organic layers were separated, and the organic phase was subsequently washed with 1N HCl (3 x 20 mL). The organic layer was then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, 5% EtOAc/Hx eluent) afforded the product as a white solid (1.90 g, 6.96 mmol, 95% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 2.5 Hz, 1H), 7.66 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.55,

163.76, 149.89, 136.86, 134.67, 125.73, 124.91, 119.18, 52.63, 21.06. HRMS (ESI) m/z calc'd for $C_{10}H_9O_4BrNa$ $[M+Na]^+$: 294.9582; found 294.9587.

Synthesis of methyl 2-acetoxy-4-allylbenzoate: To a flame-dried 3-neck round-bottom flask equipped with a stir bar and a reflux condenser was added anhydrous LiCl (1.06 g, 25 mmol, 5 eq), followed by 2-acetoxy-4-bromobenzoate (1.36 g, 5 mmol, 1 eq). The flask was placed under vacuum and purged with Ar (x 3). THF (50 mL, 0.1 M), pre-sparged with Ar for 15 min, was added to the reaction flask and then $Pd(PPh_3)_4$ (0.57 g, 0.5 mmol, 0.1 eq) and allyltributylstannane (1.70 mL, 5.5 mmol, 1.1 eq) were added sequentially. The reaction was stirred at reflux for 24 hours under an Ar atmosphere. The reaction mixture was then cooled to room temperature, diluted with EtOAc (50 mL), and quenched with an aqueous solution of 9.3% (v/v) NH_4OH (50 mL). The organic and aqueous phases were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and volatiles were removed under a stream of air in the hood overnight. Purification *via* column chromatography (SiO_2, 0% → 1% → 2% → 3% → 4% → 5% → 6% → 7% EtOAc/Hx eluent) followed by a second column chromatography (SiO_2, 5% EtOAc/Hx eluent) afforded the product as a beige-colored oil (0.83 g, 3.5 mmol, 71% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.95 (ddt, *J* = 15.8, 10.9, 6.7 Hz, 1H), 5.14 – 5.12 (m, 1H), 5.11 – 5.08 (m, 1H), 3.87 (s, 3H), 3.41 (d, *J* = 6.7 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.00, 165.12, 149.10, 138.16, 136.54, 134.16, 131.85, 123.85, 122.98, 116.85, 52.31, 39.51, 21.14. HRMS (ESI) m/z calc'd for $C_{13}H_{14}O_4Na$ $[M+Na]^+$: 257.0790; found 257.0779.

2.4.5 Mechanistic Studies

Scheme 2.21: Kinetic study



To a ½ dram vial with stir bar was added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq) Ma-SOX (6.9 mg, 0.02 mmol, 0.1 eq), 4-phenylpiperidine-borontrifluoride (45.8 mg, 0.2 mmol, 1 eq) and 2,5 dimethylbenzoquinone (30 mg, 0.22 mmol, 1.1 eq). A fresh solution of dibutyl phosphate in dioxane was added (0.2 mL), then allyl cyclohexane (31 µL, 0.2 mmol, 1 eq). The vial was sealed with Teflon tape and parafilm to prevent any liquid from escaping, then placed in a 45 °C aluminium block. The vial was stirred at 45 °C for 1-48 hours. The crude mixture was diluted with 1.0 mL of CDCl3. Trifluorotoluene (29.2 mg, 0.2 mmol, 1 eq) was added as an internal standard. 0.1 mL of the crude mixture was filtered through a celite plug flushing with 0.7 mL of CDCl3. The crude mixture was then analyzed by quantitative 1H NMR *via* Carver-Bruker 500 (500 MHz) spectrometer for the presence of 1-BF_3, 1-HBF_4, and 3-HX. Each time point is the average of three runs with error bars indicating one standard deviation (excluding of 0 hours and 48 hours which are just one run). *Experimental Note:* $Pd(OAc)_2$ was purchased from Johnson-Matthey and was "high-purity, Nitro free". Other sources of $Pd(OAc)_2$ gave variable results.

Figure 2.9: Reaction species yield over time:

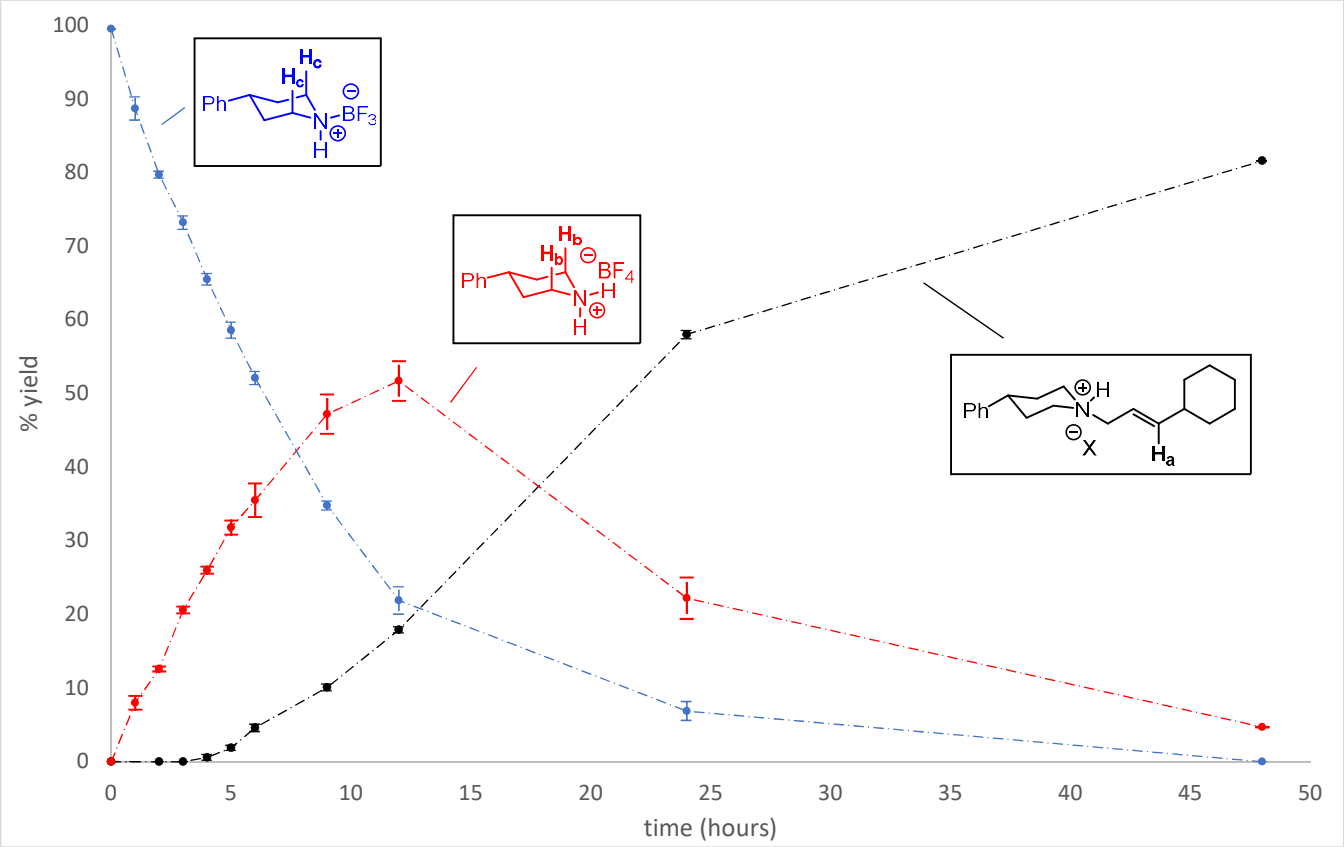
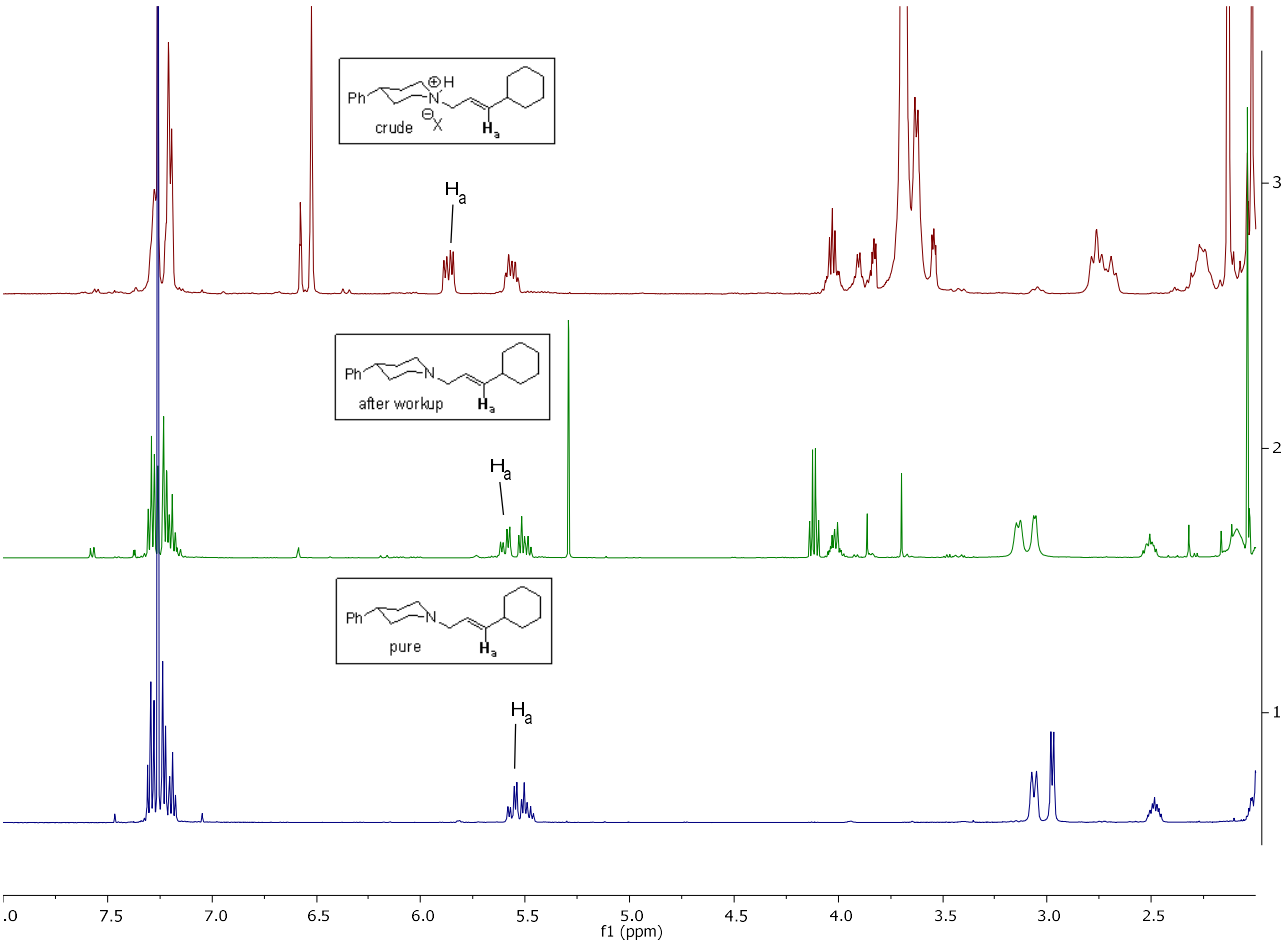
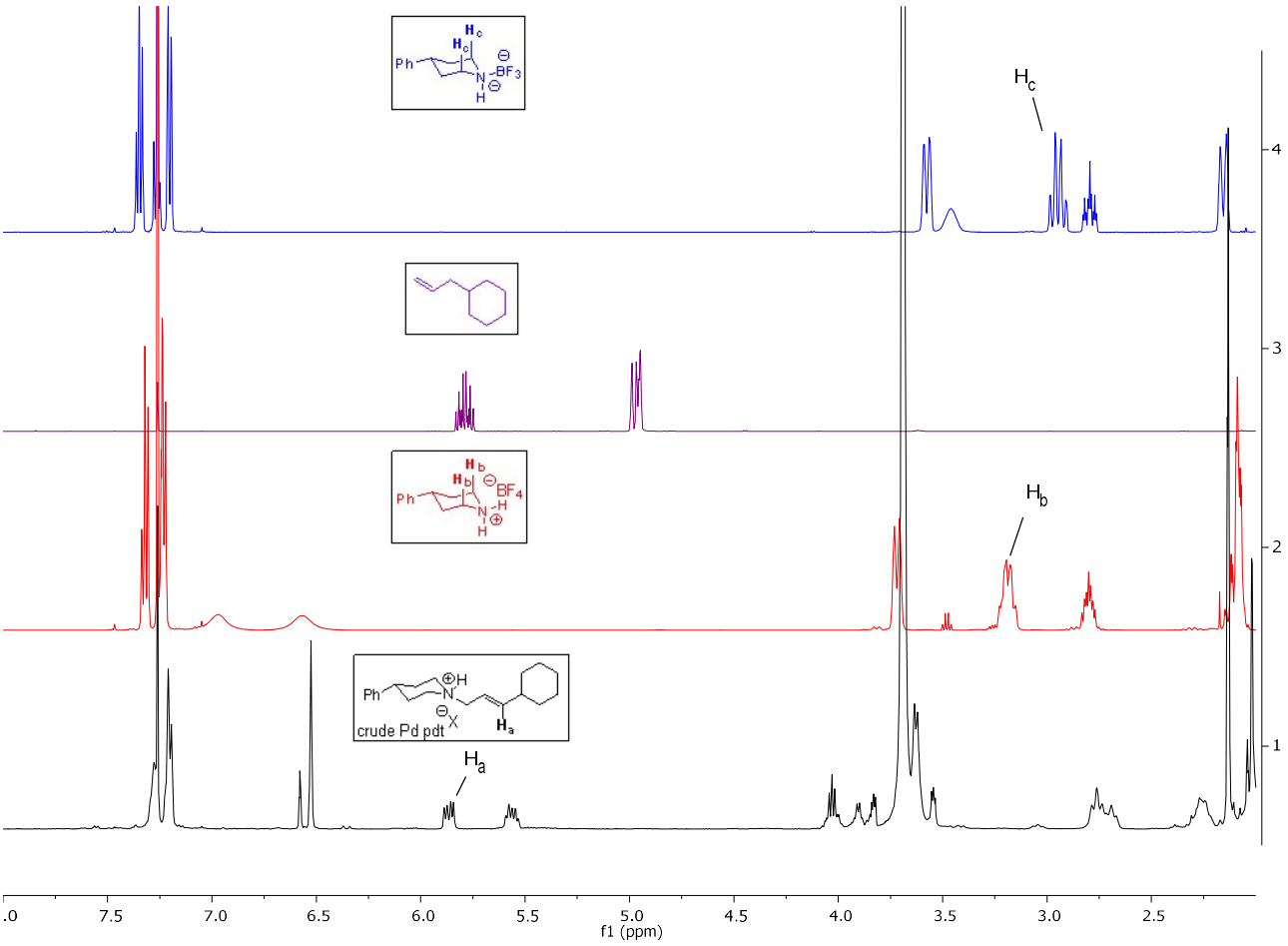


Figure 2.10: Pd Product before and after workup



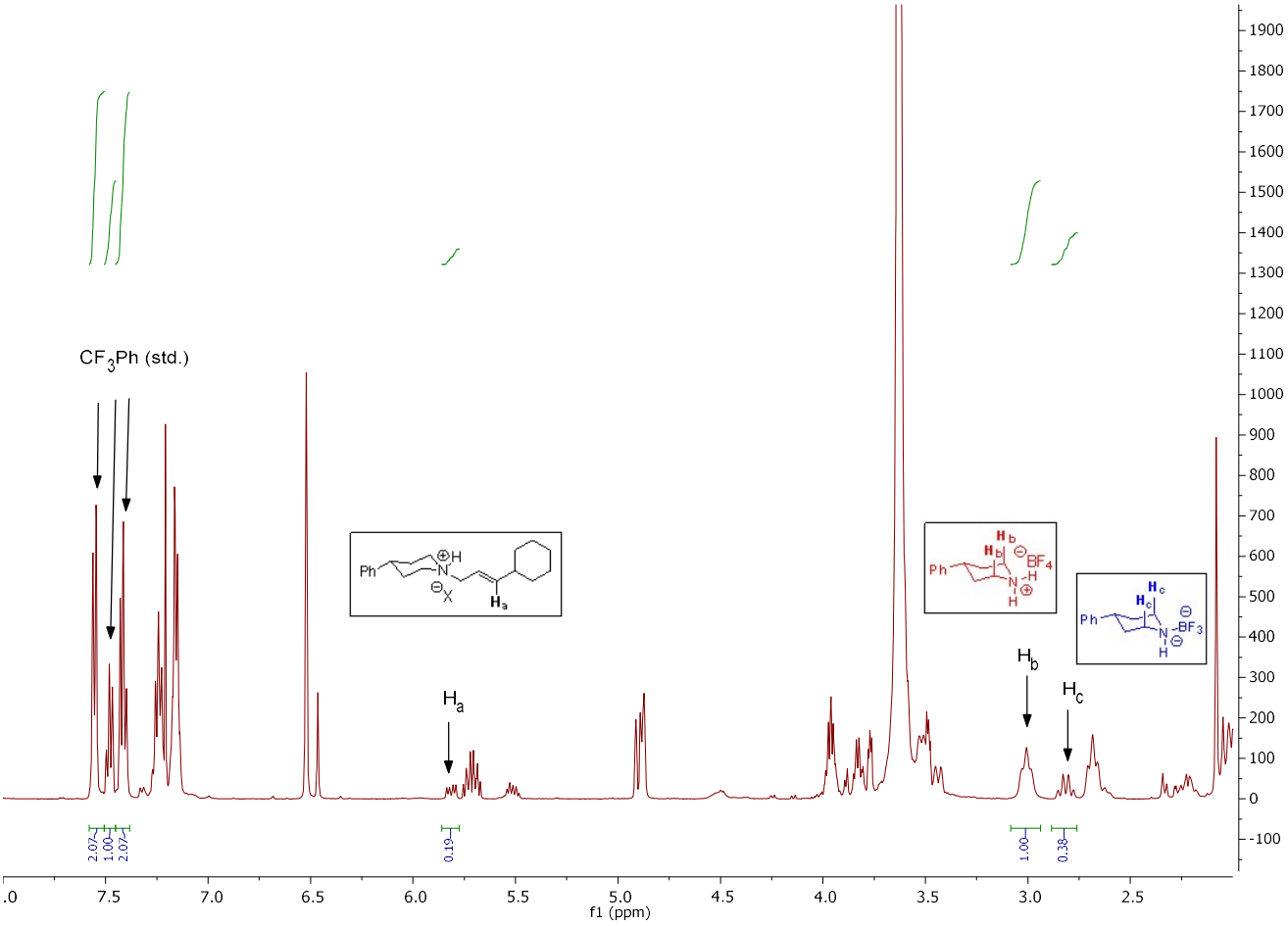
The preceding ^{1}H NMR spectra show the crude product of the Pd-reaction before and after aqueous workup. The vinylic peak (H_a) was assigned in the crude reaction by analogy to the peak in the product. The peak shifts considerably upfield due to the deprotonation of the quaternary amine.

Figure 2.11: Stacked Spectra of Reaction Species



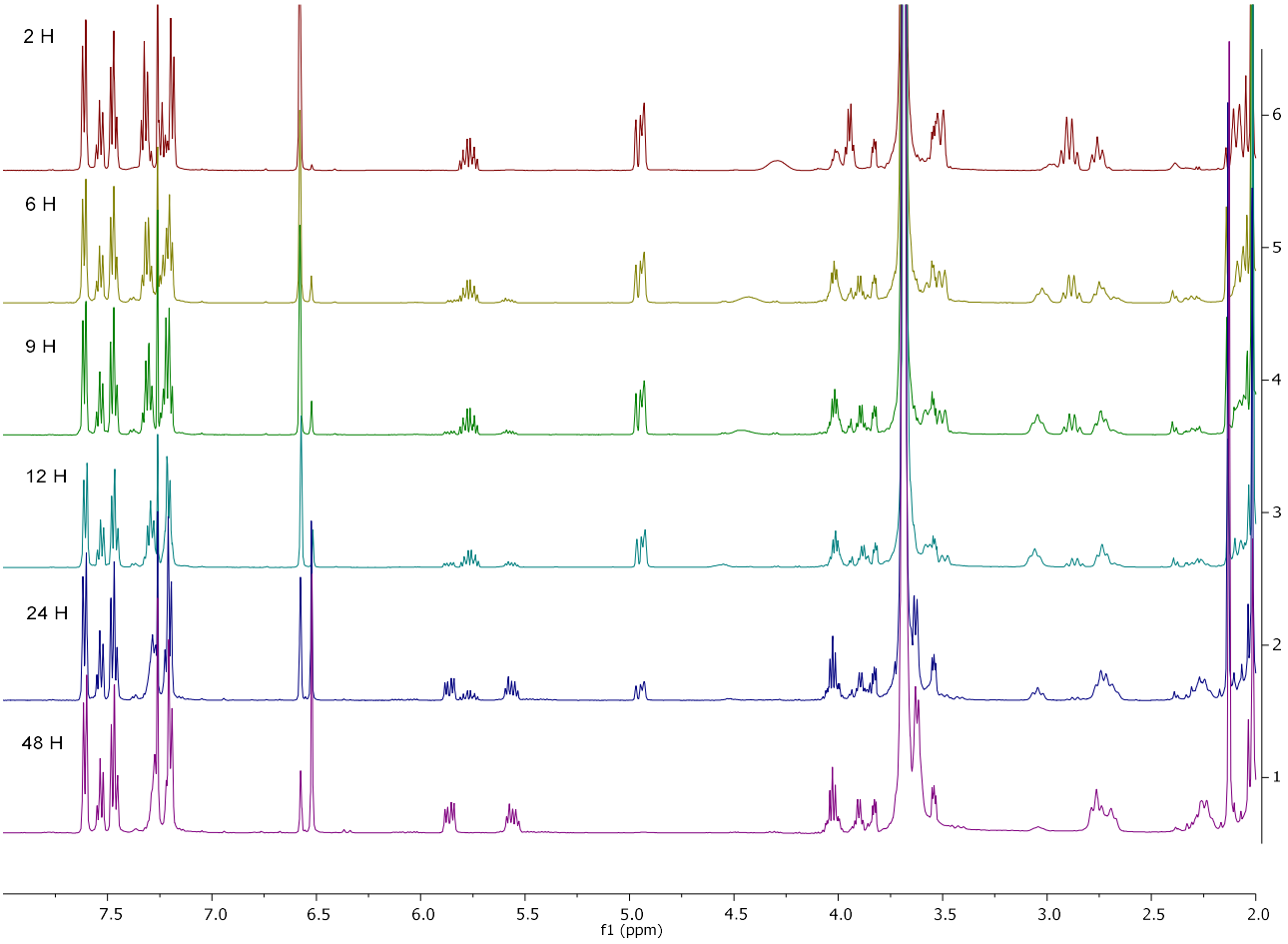
The preceding ^{1}H NMR spectra show several reaction species and assignments. Protons assigned to key intermediates are labeled.

Figure 2.12: Example Time point: 12 hours



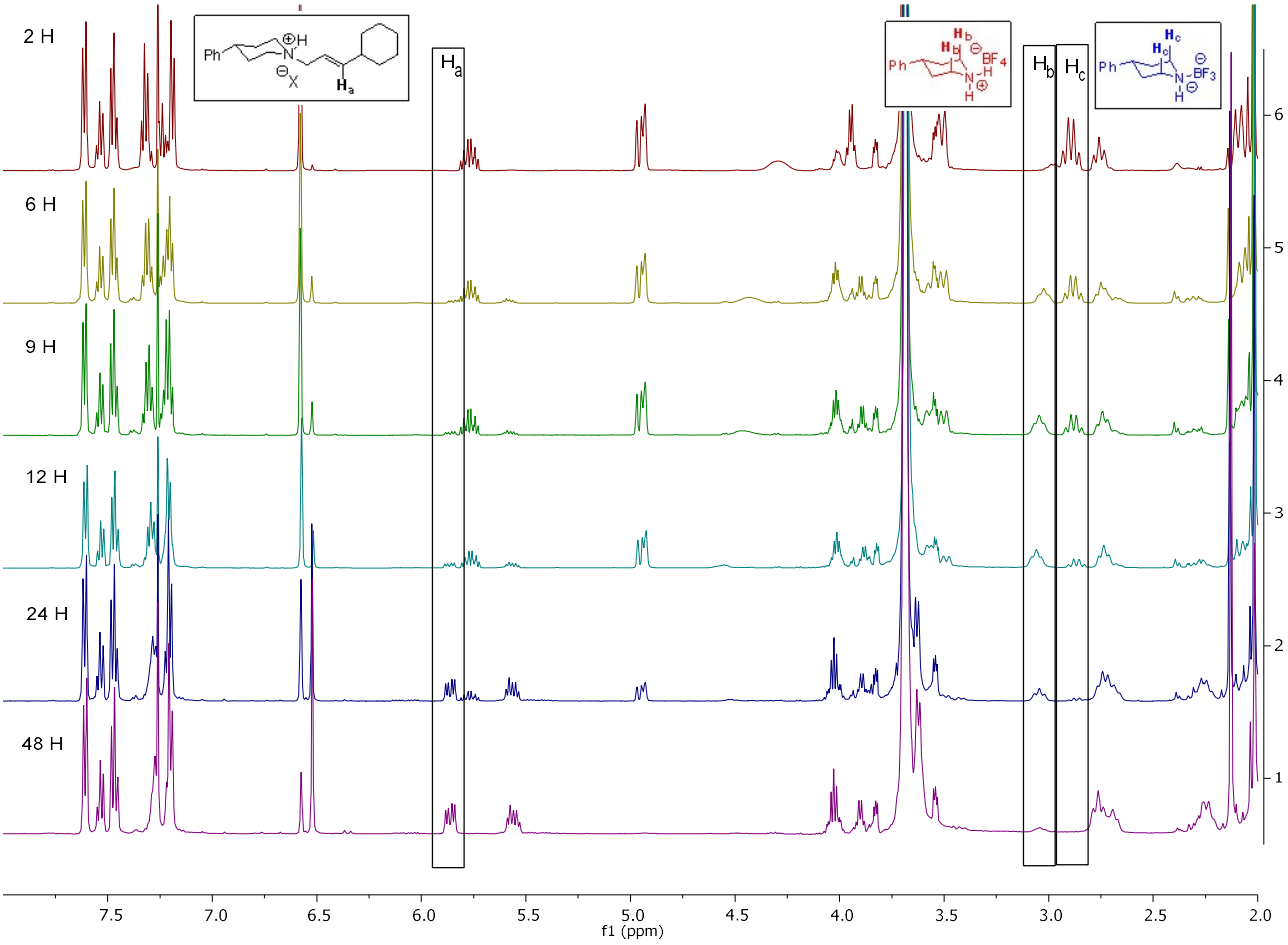
The preceding ^{1}H NMR spectrum shows an example of a crude product mixture taken at the 12-hour time point. Protons assigned to key intermediates are labeled with integrals.

Figure 2.13a: Stacked Time Series (no annotations)



The preceding selected ^{1}H NMR spectra show the crude reaction mixture over time.

Figure 2.13b: Stacked Time Series (annotated)



The preceding selected ^{1}H NMR spectra show the crude reaction mixture over time. Protons assigned to key intermediates are labeled.

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